reaction mixture was quenched with water (200 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were then washed with H_2O (2 x 200 mL), and saturated aqueous NaCl solution (100 mL), and dried over $MgSO_4$. The solvents were then removed *in vacuo*, and the residual pale-yellow oil was purified by flash column chromatography (0–15% EtOAc-hexane gradient elution) to afford aldehyde 103 (10.2 g; 52%) as a pale-yellow solid.

Synthesis of bromide 104

A solution aldehyde **103** (4.91 g, 26.4 mmol) in methanol (120 mL) was treated with sodium borohydride (1.18 g, 31.7 mmol) at 0–5°C, and the resulting reaction mixture was stirred at 0–5°C for an additional 1 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was quenched with water (20 mL). The solvents were then removed *in vacuo*, and the residue was directly purified by flash column chromatography (5–25% EtOAc-hexane gradient elution) to afford bromide **104** (4.23 g; 85%) as a white solid.

Synthesis of alcohol 105

A solution of boronate **81** (11.05 g, 29.2 mmol) and bromide **104** (4.227 g, 22.5 mmol) in toluene (150 mL) was treated with solid potassium carbonate (9.315 g, 67.5 mmol), ethanol (50 mL) and H_2O (50 mL) at room temperature, and the resulting reaction mixture was degassed three times under a steady stream of argon before being treated with $Pd(dppf)_2Cl_2$ (564 mg, 0.675) at room temperature. The reaction mixture was then degassed three times again under a steady stream of argon before being warmed up to reflux for 1 h. When LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature before being treated with water (200 mL) and ethyl acetate (100 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water (2 x 50 mL) and saturated aqueous NaCl solution (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford alcohol **105** (6.16 g; 76%) as a grey solid.

Synthesis of azide 107

A suspension of alcohol **105** (2.15 g, 6.0 mmol) in CH_2Cl_2 (25 mL) was treated with diisopropylethylamine (1.551 g, 2.10 mL, 12.0 mmol) and methanesulfonyl chloride (756 mg, 0.511 mL, 6.6 mmol) at 0–5°C, and the resulting reaction mixture was stirred at 0-5°C for an

additional 2 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was treated with water (20 mL) and CH_2Cl_2 (40 mL). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were washed with water (20 mL) and saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford mesylate **106** (2.47 g; 94%) as a yellow solid.

A solution of mesylate **106** (874 mg, 2.0 mmol) in DMF (8.0 mL) was treated with sodium azide (260 mg, 4.0 mmol) at room temperature, and the resulting reaction mixture was warmed up to 40-45°C for 3 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was treated with water (20 mL), and the precipitate was collected by filtration, washed with water (2 x 10 mL), and dried *in vacuo* to afford crude azide **107** (699 mg; 91%) as a grey solid, which was of suitable purity for use in subsequent reactions.

Synthesis of amine 108

A suspension of azide **107** (2.611 g, 6.8 mmol) in THF (25 mL) was treated with water (0.13 mL, 68 mmol) and triphenylphosphine (PPh_3, 2.14 g, 8.2 mmol) at room temperature, and the resulting reaction mixture was subsequently stirred at room temperature for 12 h. When TLC and LCMS showed that the reaction was complete, the solvents were removed *in vacuo*, and the residue was directly purified by flash column chromatography (0-15% MeOH-CH_2Cl_2 gradient elution) to afford amine **108** (2.233 g; 92%) as a yellow solid.

Synthesis of tetrazole 1035

A solution of amine **108** (90 mg, 0.25 mmol) in acetic acid (3.0 mL) was treated with triethyl orthoformate (0.1 mL) and sodium azide (40 mg) at room temperature, and the resulting reaction was subsequently stirred at reflux for 4 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature and concentrated *in vacuo*. The residue was then directly purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford tetrazole **1035** (43 mg; 36%) as a white solid. LCMS (ESI) *m/z* 412 $(M + H)^+$.

Synthesis of triazole 1036

A solution of azide **107** (142 mg, 0.37 mmol) in DMF (5 mL) was treated with thimethylsilyl acetylene (0.5 mL) at room temperature, and the resulting reaction mixture was

subsequently stirred at 70–80°C for 12 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature before being concentrated *in vacuo*. The residue was then directly purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford triazole **109** (152 mg; 85%) as a pale-yellow oil, which was directly used in the subsequent reaction.

A solution of triazole **109** (152 mg, 0.315 mmol) in THF (10 mL) was treated with a 1N solution of tetrabutylammonium fluoride in THF (2.0 mL) at 0–5°C, and the resulting reaction mixture was stirred at 0–5°C for 1 h before being gradually warmed up to room temperature for 10 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature before being concentrated *in vacuo*. The residue was then directly purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford triazole **1036** (67 mg; 52%) as a pale-yellow oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 411 $(M + H)^+$.

Example 16 - Synthesis of Triazole 1037

A solution of mesylate **52** (436 mg, 1.0 mmol) in anhydrous DMF (5 mL) was treated with 1,2,4-triazole sodium salt (182 mg, 2.0 mmol) at 0–5°C, and the resulting reaction mixture was stirred at 0–5°C for 1 h before being gradually warmed up to room temperature for 10 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was then directly purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford triazole **1037** (388 mg; 95%) as a white solid. LCMS (ESI) *m/z* 410 $(M + H)^+$.

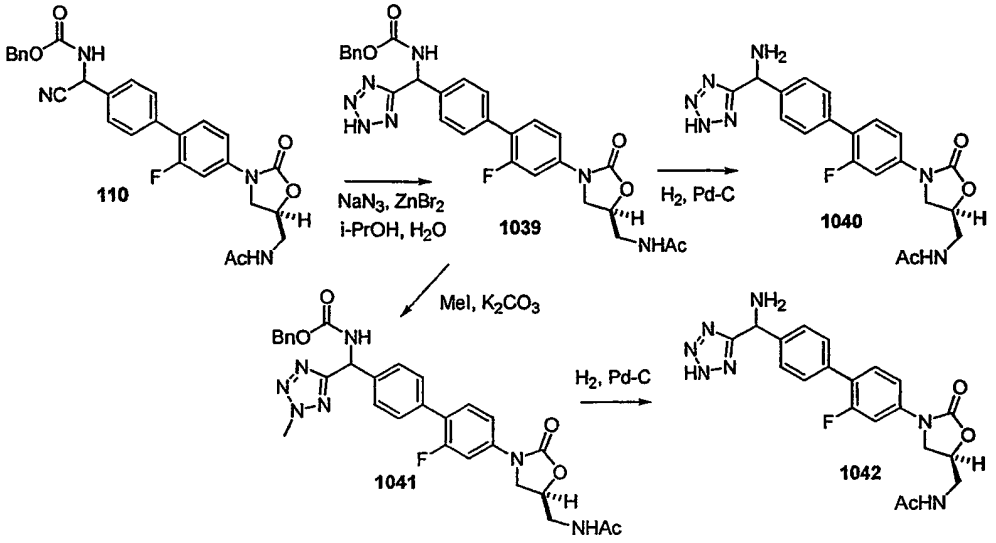
Example 17 - Synthesis of Piperazine 1038

A suspension of the aldehyde **92** (142 mg, 0.4 mmol) in MeOH (4.0 mL) and THF (1.0 mL) was treated with 1-(3-chloro-5-trifluoromethyl-pyridin-2-yl)piperazine (106 mg, 0.4 mmol) and sodium triacetoxyborohydride (160 mg, 0.8 mmol) at 25°C, and the resulting reaction mixture was stirred at 25°C for 6 h. When TLC and LCMS showed the reductive amination reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford piperazine **1038** (38 mg; 16% yield) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 607 $(M + H)^+$.

Example 18 – Synthesis of Tetrazoles 1039-1042

Scheme 15 shows the synthesis of compounds **1039-1042**. Nitrile **110** is converted to tetrazole **1039**, which was deprotected to afford tetrazole **1040**. Tetrazole **1039** is methylated to afford **1041**, which was subsequently deprotected to yield **1042**.

Scheme 15



Synthesis of nitrile 110

A suspension of aldehyde **92** (1.884 g, 5.3 mmol) in MeOH (25 mL) was treated with a solution of NaCN (312 mg, 6.4 mmol) in H_2O (10 mL) and a solution of ammonium chloride (340 mg, 6.4 mmol) in H_2O (15 mL) at 25°C, and the resulting mixture was stirred at 25°C for 30 min before being warmed up to 50°C for 1 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature before being treated with H_2O (25 mL) at 25°C, and the resulting mixture was cooled down to 0–5 °C for 1 h. The solid precipitates were collected by filtration, washed with H_2O (2 x 20 mL) and 20% EtOAc/hexane (2 X 20 mL), and dried *in vacuo*. The crude desired *N*-{3-[4'-(amino-cyano-methyl)-2-fluoro-biphenyl-4-yl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (1.801 g; 89% yield) was obtained as off-white solids, which by HPLC and ^{1}H NMR was of sufficient purity to be used in subsequent reactions. LCMS (ESI) *m/z* 383 $(M + H)^+$.

A solution of *N*-{3-[4'-(amino-cyano-methyl)-2-fluoro-biphenyl-4-yl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide obtained above (1.70 g, 4.45 mmol) in THF (40 mL) and H_2O (40 mL) was treated with benzyl chloroformate (940 mg, 5.34 mmol) and potassium carbonate (1.23 g, 8.9 mmol) at 25°C, and the resulting reaction mixture was stirred at 25°C for

2 h. When TLC and LCMS showed the reaction was complete, the reaction mixture was quenched with H_2O (20 mL) and EtOAc (50 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (50 mL). The combined organic extracts were washed with water (2 x 20 mL), and saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was then purified by column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford the desired nitrile **110** (2.20 g; 96%) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. This material by ^1H NMR was found to be a mixture of two diastereomers. LCMS (ESI) *m/z* 517 $(M + H)^+$.

Synthesis of tetrazole 1039

A solution of 0.130 g (2.52 mmol) of nitrile **110**, 0.033 g (5.04 mmol) of NaN_3, and 0.028 g (1.26 mmol) of zinc bromide ($ZnBr_2$) in 9 ml of isopropanol/H_2O (1:2) was allowed to stir at reflux for 24 h. Once the reaction mixture cooled down, it was diluted with 1 N HCl, extracted with MeOH/CH_2Cl_2 (1:3) (40 ml x 3), and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to give 0.050 g of tetrazole **1039** as a mixture of tautomers. LCMS (ESI) *m/z* 560 $(M + H)^+$.

Synthesis of tetrazole 1040

A solution of 0.030 g of **1039** and 0.020 g of palladium on carbon (Pd/C) (10%) in 6 ml of (1:1 H_2O/THF) was allowed to stir at 25°C under H_2 atmosphere (balloon) for 16 h. The reaction mixture was filtered through celite, and washed with MeOH/CH_2Cl_2. The filtrate was concentrated, washed with small amount of EtOAc, then dried via vacuum to give 0.010 g of tetrazole **1040**. LCMS (ESI) *m/z* 426 $(M + H)^+$.

Synthesis of methyl tetrazole 1041

A solution of 0.218 g (0.39 mmol) of **1039**, 0.080 g (0.58 mmol) of K_2CO_3, and 0.061 g (0.43 mmol) of methyl iodide (MeI) in 5 ml of DMF was allowed to stir at 25°C for 16 h. The reaction solvent was removed by vacuum. The residue was dissolved in a mixture of MeOH/CH_2Cl_2 (1:1), filtered through a pipette column, and the filtrate was concentrated to give the crude product **1041** in the amount of about 0.220 g. A small amount was purified through preparative HPLC. LCMS (ESI) *m/z* 574 $(M + H)^+$.

Synthesis of methyl tetrazole 1042

A solution of 0.220 g of **1041** and 0.020 g of Pd (10% on carbon) in 3 ml of DMF was allowed to stir at 25°C under H_2 atmosphere (balloon) for 24 h. The solvents were removed by

rotary evaporation, the residue was then dissolved in a mixture of MeOH/CH_2Cl_2, and filtered through celite. The filtrate was concentrated and further purified by preparative HPLC to give 0.052 g of methyl tetrazole **1042**. LCMS (ESI) *m/z* 440 $(M + H)^+$.

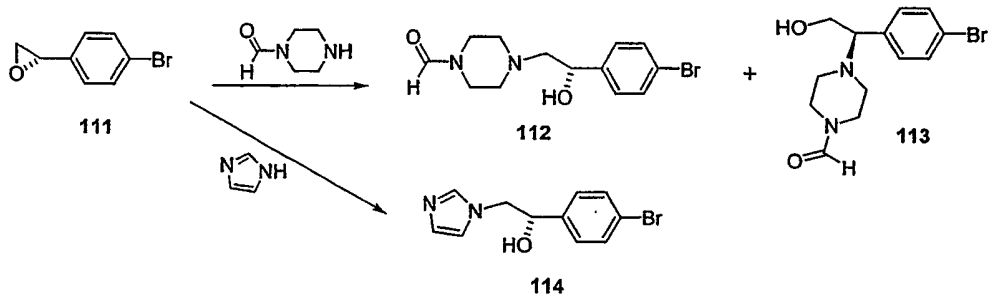
Example 19 – Synthesis of Pyrazole 1043

To a suspension of 0.048 g (2.0 mmol) of NaH and 0.125 g (1.83 mmol) of pyrazole in 8 ml of DMF at 0°C was added 0.400 g (0.92 mmol) of mesylate **52**. Then, the reaction mixture was warmed up to 25°C, and was allowed to stir for 3 h. The DMF was removed and the residue was purified by preparative TLC to give 0.360 g of pyrazole **1043** (96% yield). LCMS (ESI) *m/z* 409 $(M + H)^+$.

Example 20 – Synthesis of Compounds 1044-1046

Scheme 16 depicts the synthesis of aryl bromides **112-114** required for the synthesis of compounds **1044-1046**. Epoxide **111** was treated with 1-formyl piperazine to afford a mixture of **112** and **113**. Epoxide ring-opening of **111** with imidazole afforded **114**. These bromides were coupled with boronate **81** to deliver the target compounds **1044-1046**.

Scheme 16



Synthesis of epoxide 111

To a solution of 4-bromostyrene (5.00 g, 26.8 mmol) in CH_2Cl_2 (130 mL) was added 4-methylmorpholine *N*-oxide (NMO, 12.90 g, 107.1 mmol, anhydrous) and Jacobsen catalyst ((1S, 2S)-(+)-[1,2-(cyclohexanodiamino-N,N'-bis(3,5-di-t-butyl-salicylidene)] manganese(III) chloride, 850 mg, 1.34 mmol). The solution was cooled to -78°C, then *m*-chloroperbenzoic acid (*m*-CPBA, 7.40 g, 42.8 mmol) was added in four portions every 10 min. The mixture was stirred at -78°C for 2 h. The reaction was quenched by addition of sodium thiosulfate ($Na_2S_2O_3$) solution (10.0 g in 30 mL water), then the cooling bath was removed, and water (70 mL), 1N sodium hydroxide (NaOH, 60 mL) was added. The aqueous phase was extracted with

CH_2Cl_2 (30 mL x 3), dried with Na_2SO_4, and evaporated. The residue was purified by flash chromatography (4:100 Et_2O/Hexane) to yield 5.20 g epoxide **111** (98% yield).

General procedure for the synthesis of bromides 112-114 from epoxide 111

To a suspension of epoxide **111** (1mmol, 1eq) in acetonitrile (3.0 mL) at room temperature was added lithium perchlorate ($LiClO_4$, 1.05 mmol, 1.05 eq). After the formation of a clear solution, the amine (1.5 mmol, 1.5 eq) was added. The mixture was stirred at room temperature or at 60°C. The solvent was removed under vacuum and the residue was purified by flash chromatography.

Conditions for 112 and 113: room temperature, 16 h, flash chromatography (3:100 MeOH/CH_2Cl_2). Yield of **112**: 132 mg; Yield of **113**: 42 mg.

Conditions for 114: 60°C, 4 h, flash chromatography (3:100 MeOH/CH_2Cl_2). Yield of **114**: 103 mg.

General procedure for the synthesis of compounds 1044-1046 from bromides 112-114

A suspension of bromide intermediate (1 eq), boronate **81** (1 eq), $PdCl_2(dppf)_2$ (0.05 eq), and K_2CO_3 (4 eq) in a mixture of dioxane/EtOH/H_2O (ratio of 3:1:1) was degassed by a stream of argon. The mixture was stirred at 75°C to 85°C for 3 to 15 h. The solvent was removed by vacuum and the residue was purified by flash chromatography to afford the product.

Conditions for 1044: 80°C, 3.5 h, flash chromatography (4:100 MeOH/CH_2Cl_2); Yield 150 mg. LCMS (ESI) *m/z* 485 $(M + H)^+$.

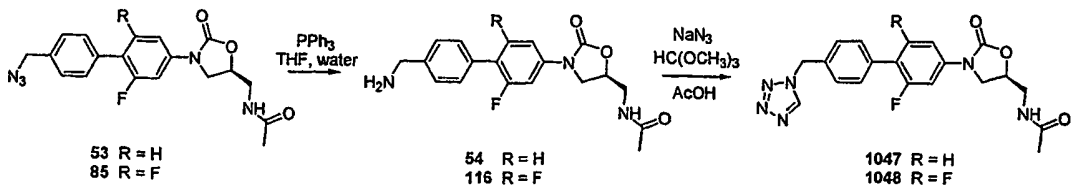
Conditions for 1045: 80°C, 3.5 h, flash chromatography (5:100 MeOH/CH_2Cl_2); Yield 52 mg. LCMS (ESI) *m/z* 485 $(M + H)^+$.

Conditions for 1046: 80°C, 2.5 h, flash chromatography (10:100 MeOH/CH_2Cl_2); Yield 155 mg. LCMS (ESI) *m/z* 439 $(M + H)^+$.

Example 21 – Synthesis of Compounds 1047 and 1048

Scheme 17 depicts the synthesis of tetrazoles **1047** and **1048**. Azides **53** and **85** were reduced to amines **115** and **116** respectively. These amines were then converted to triazoles **1047** and **1048** by treatment with sodium azide and trimethylorthoformate in hot acetic acid.

Scheme 17



Synthesis of amine 54

Amine **54** was prepared from azide **53** according to the method described in Example 1.

Synthesis of amine 116

Azide **85** (1.10 g, 2.74 mmol) was dissolved in 17 mL THF and 0.6 mL water. Triphenylphosphine (1.30 g, 4.96 mmol) was added, and the mixture was heated to reflux for 4 h. The mixture was allowed to stir overnight at room temperature, and was partitioned between ethyl acetate and 20 mL 2N aqueous HCl. The organic layer was extracted with 20 mL 2N aqueous HCl, and then the aqueous layer was basified with 85 mL 1N aqueous NaOH. The cloudy aqueous phase was extracted with ethyl acetate (2 x), and 5% methanol/methylene chloride (2 x). The combined organic extracts were dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel using a gradient elution of methylene chloride then methanol/methylene chloride (up to 10% methanol) to afford amine **116** (0.587 g, 1.57 mmol; 57%) as a tan solid. LCMS (ESI) *m/z* 376 $(M + H)^+$.

Synthesis of tetrazole 1047

A solution of amine **54** (0.20 g, 0.56 mmol) in acetic acid (5 mL) was treated with sodium azide (0.05 g, 0.84 mmol) followed by triethylorthoformate (0.15 mL, 0.90mmol). The reaction mixture was heated to reflux for 4 h. The mixture was cooled and added to ice water (10 mL). After standing at room temperature for 48 h, the precipitated product was collected by filtration and washed with cold CH_3OH to yield tetrazole **1047** (101mg; 50%) as a white solid. LCMS (ESI) *m/z* 474 $(M + H)^+$.

Synthesis of tetrazole 1048

Tetrazole **1048** was made from amine **116** using the same procedure for the synthesis of **1047**. LCMS (ESI) *m/z* 429.

Example 22 – Synthesis of Compounds 1049-1054

Synthesis of 1049

A solution of mesylate **52** (0.10 g, 0.24 mmol) in dimethyl sulfoxide (DMSO, 2.0 mL) was treated with ethyl 4-pyrazole carboxylate (0.03 g, 0.24 mmol), K_2CO_3 (0.06 g, 0.46 mmol) and the mixture was heated to 90°C for 16 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL), and washed with brine (2 x 50 mL). The organic phase was dried and evaporated. The residue was purified by preparative thin layer chromatography (using 95% CH_2Cl_2, 5% MeOH as eluant) to provide **1049**. LCMS (ESI) *m/z* 481 $(M + H)^+$.

Synthesis of 1050

This compound was made from mesylate **52** and 4-(hydroxymethyl)imidazole using the same procedure described for the synthesis of **1049**. LCMS (ESI) *m/z* 439 $(M + H)^+$.

Synthesis of 1051

This compound was made from mesylate **52** and 4-pyrazolecarboxylic acid using the same procedure described for the synthesis of **1049**. LCMS (ESI) *m/z* 453 $(M + H)^+$.

Synthesis of 1052

This compound was made from mesylate **52** and 4-methylpyrazole using the same procedure described for the synthesis of **1049**. LCMS (ESI) *m/z* 423 $(M + H)^+$.

Synthesis of 1053

This compound was made from mesylate **52** and 3-aminopyrazole using the same procedure for the synthesis of **1049**. LCMS (ESI) *m/z* 424 $(M + H)^+$.

Synthesis of 1054

This compound was made from mesylate **52** and pyrrole using the same procedure for the synthesis of **1049**. LCMS (ESI) *m/z* 408 $(M + H)^+$.

Example 23 – Synthesis of Aldehyde 1055

A solution of amine **54** (0.20 g, 0.56 mmol) in acetic acid (5 mL) was treated with 2,5-dimethoxy-3-tetrahydrofurancarboxaldehyde (0.12 g, 0.78 mmol). The reaction mixture was heated to reflux for 2 h. The mixture was cooled and the solvent removed under high vacuum.

The residue was purified by preparative thin layer chromatography (using 95% CH_2Cl_2, 5% MeOH as eluant) to provide **1055**. LCMS (ESI) *m/z* 436 $(M + H)^+$.

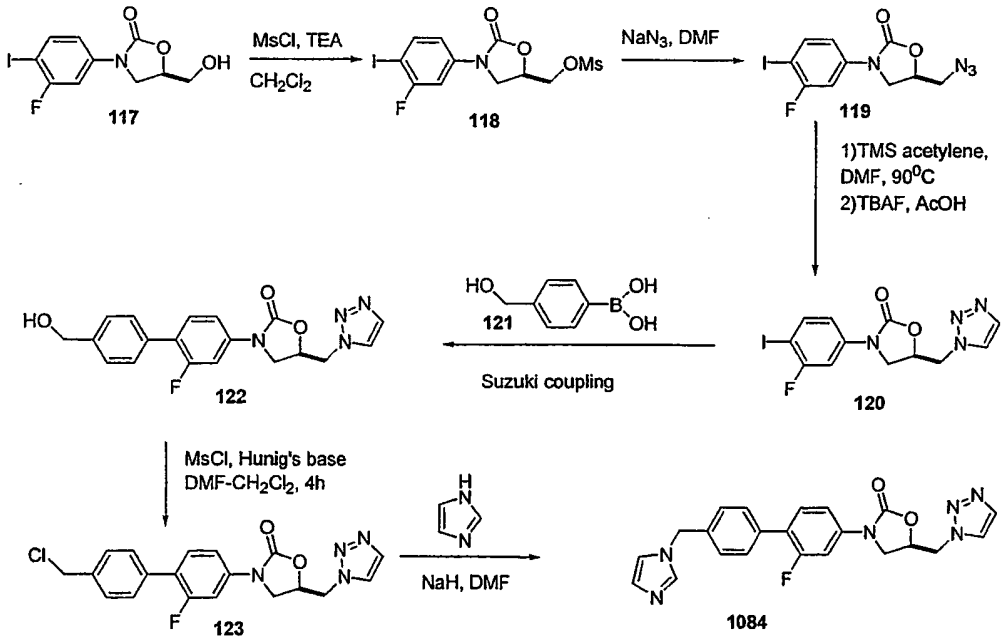
Example 24 – Synthesis of Tetrazole 1056

A solution of mesylate **52** (0.50 g, 1.14 mmol) in acetonitrile (CH_3CN, 5 mL) was treated with tetrazole (12 mL, 5.73 mmol), and triethylamine (0.8 mL, 5.73 mmol), and the mixture was heated to reflux for 18 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (100 mL), and washed with brine (2 x 50 mL). The organic phase was dried and evaporated. The residue was purified by preparative thin layer chromatography (using 95% CH_2Cl_2, 5% MeOH as eluant) to provide **1056**. LCMS (ESI) *m/z* 411.

Example 25 - Synthesis of Imidazole 1084

Scheme 18 depicts the synthesis of imidazole **1084**.

Scheme 18



Synthesis of iodide 120

To a suspension of alcohol **117** (5 g, 14.84 mmol) in CH_2Cl_2 (80 mL) was added triethyl amine (2.5 mL, 17.8 mmol) and methanesulphonyl acid chloride (1.4 mL, 17.8 mmol) at 0 °C and stirred the clear solution for 1 h at the same temperature. The reaction mixture was poured into brine solution (100 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined

organic layer was washed with brine solution (3 x 100 mL), dried over anhydrous Na_2SO_4, and concentrated to yield mesylate **118**. To this was added NaN_3 (2 g, 29.7 mmol) and DMF (50 mL) and the mixture was heated to 80 °C overnight. The solution was poured into a mixture of ethyl acetate (150 mL) and water (100 mL). The organic layer was separated and the aqueous portion was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (1 x 150 mL), dried over anhydrous Na_2SO_4, and concentrated to yield 5.4 g of azide **119**.

A solution of aizde **119** (5.4 g, 14.84 mmol) and trimethylsilyl acetylene (10.48 mL, 74.2 mmol) in DMF (20 mL) was heated to 90 °C for 12 h. The reaction mixture was concentrated and treated with TBAF (60 mL, 1M in THF) and acetic acid (2 mL, 29.7 mmol) and stirred at ambient temperature for 12 h. The solution was concentrated and poured into a mixture of saturated NH_4Cl (50 mL), ethyl acetate (150 mL) and brine solution (50 mL). The organic layer was separated and the aqueous portion was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated and the solid thus obtained was washed with water (5 x 200 mL) to yield 5.7 g of tetrazole derivative **120**. LCMS (ESI) m/e 389 ($M+H^+$).

Synthesis of alcohol 122

To a mixture of tetrazole **120** (5.7 g, 14.84 mmol), boronic acid **121** (2.9 g, 19.29 mmol), K_2CO_3 (6.0 g, 44.52 mmol) and $Pd(PPh_3)_4$ (857 mg, 5 mol %) was added toluene (120 mL), ethyl alcohol (40 mL) and water (40 mL). The reaction mixteure was degassed, flushed with argon, and refluxed for 4 h. The solvent was concentrated under reduced pressure and the residue thus obtained was poured into water (2000 mL). The pale yellow solid was filtered, and dried at 40 °C under vacuum to yield 4.76 g of alcohol **122**. LCMS (ESI) m/e 369 ($M+H^+$).

Synthesis of chloride 123

To a solution of alcohol **122** (4.6 g, 12.5 mmol) and Hunig's base (6.4 mL, 38.75 mmol) in DMF (40 mL) and CH_2Cl_2 (30 mL) was added methanesulphonyl chloride (2.9 mL, 37.5 mmol) at 0 °C, and the resulting solution was stirred at ambient temperature for 3 h. The solution was concentrated to remove the CH_2Cl_2 and poured into water (1000 mL). The pale yellow solid was filtered and successively washed with water (5 x 200 mL), 10% ethyl acetate in hexanes (5 x 100 mL) and 50% ether in hexanes (5 x 100 mL). The resulting solid was dried at 40 °C under vacuum to yield 4.5 g of chloride **123**. LCMS (ESI) m/e 387 ($M+H^+$).

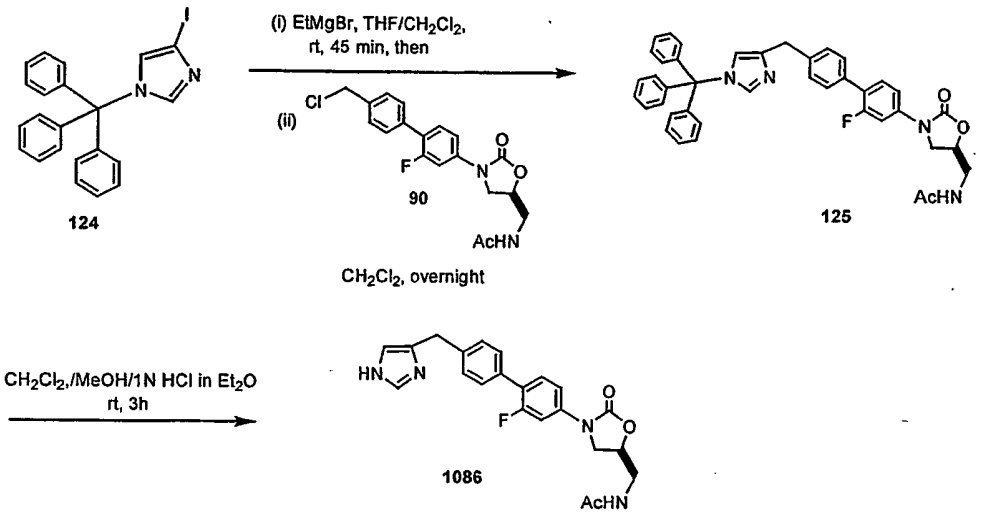
Synthesis of 1084

To a solution of imidazole (31 mg, 0.224 mmol) in DMF (3 mL) was added NaH (17 mg, 0.448 mmol) at 0 °C, and the solution was stirred for 20 min at 0 °C. Chloride **123** was added and the reaction was stirred at ambient temperature for 90 min. The reaction mixture was concentrated and purified by flash chromatography over silica gel (96:4 CH_2Cl_2/MeOH) to yield 65 mg of **1084**. LCMS (ESI) m/e 419 ($M+H^+$).

Example 26 - Synthesis of Imidazole 1086

Scheme 19 depicts the synthesis of imidazole **1086**.

Scheme 19



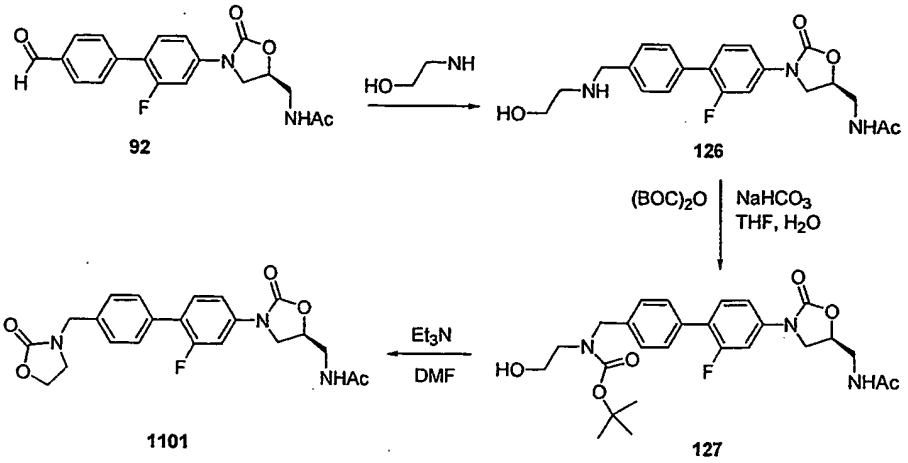
To a solution of imidazole **124** (0.25g, 0.56 mmol) in dry CH_2Cl_2 (3 mL) was added 1M ethyl magnesium bromide (EtMgBr) in THF (0.62 mL, 0.62 mmol) at room temperature. After stirring for 45 min, oxazolidinone **90** (0.233g, 0.62 mmol) was added to the mixture and stirring continued overnight. The reaction was quenched with aqueous NH_4Cl (20 mL), extracted with CH_2Cl_2 (25 mL) and dried over Na_2SO_4. The solvent was evaporated to yield **125** as a solid residue. The crude was dissolved in 10 % MeOH in CH_2Cl_2 (10 mL), and 1N HCl in diethyl ether (2 mL, 2 mmol) was added, followed by stirring for 3h. The solvent was evaporated and the residue was partitioned between dilute NH_4OH (30 mL) and CH_2Cl_2 (30 mL). The layers were separated, the aqueous layer was back extracted with CH_2Cl_2 (2 X 30 mL), and the combined organic layer was dried over Na_2SO_4. The solvent was evaporated and the crude product was purified on silica gel column, eluting with 1- 8 % MeOH in CH_2Cl_2 to

yield imidazole **1086** as a thick oil which precipitated to white solid in diethyl ether (0.051g, 22 %). LCMS (ESI) m/e 409.0 $(M+H)^+$.

Example 27 - Synthesis of Compound 1101

Scheme 20 depicts the synthesis of compound **1101**.

Scheme 20



Synthesis of alcohol 126

To a stirred solution of 0.050 g (0.14 mmol) of aldehyde **92** and 0.010 g (0.17 mmol) of aminoethanol in 5 ml of DMF was added 0.059 g (0.28 mmol) of $NaB(OAc)_3H$. The reaction mixture was stirred for 2 h. DMF was removed *in vacuo*, and the residue was purified by preparative TLC to give 0.055 g of alcohol **126**. MS (M+1): 438.

Synthesis of alcohol 127

A solution of 0.050 g (0.11 mmol) of **126**, 0.030 g (0.14 mmol) of $(BOC)_2O$, 0.038 g (0.46 mmol) of $NaHCO_3$ in 10 ml of THF:H_2O (4:1) was stirred at 25 °C for 6 h. The reaction mixture was diluted with water (30 ml) and extracted with CH_2Cl_2 (50 ml x 3). The combined organic layers were washed with brine (40 ml), dried over $MgSO_4$, and concentrated to give 0.040 g of alcohol **127**. MS (M+1): 501.

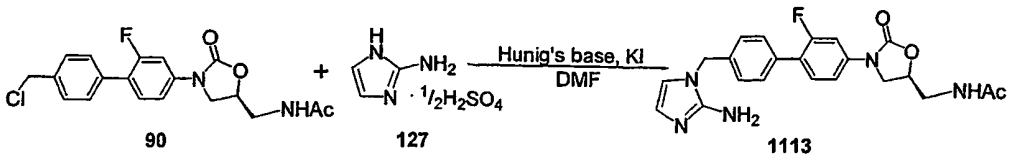
Synthesis of compound 1101

A solution of 0.126 g (0.25 mmol) of alcohol **127** and 0.11 ml (0.75 mmol) of Et_3N in 5ml of DMF was heated to 60 °C for 24 h. The reaction mixture was cooled and the solvent was removed *in vacuo*. The residue was purified via preparative TLC to yield 0.033 g of compound **1101**. MS (M+1): 428.

Example 28 - Synthesis of Imidazole 1113

Scheme 21 depicts the synthesis of imidazole **1113**.

Scheme 21



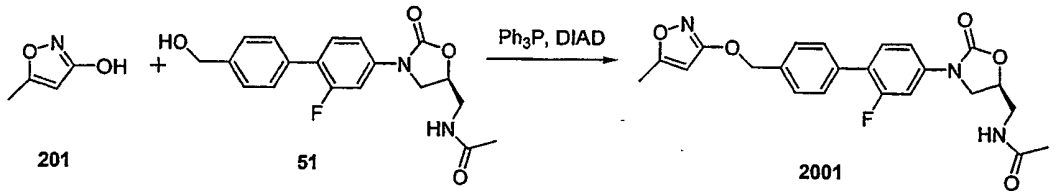
90 127 1113

A mixture of chloride **90** (113 mg, 0.3 mmol), 2-aminoimidazole sulfate **127** (119 mg, 0.9 mmol), N,N-diisopropylethylamine (0.26 mL, 1.5 mmol) and KI (17 mg, 0.1 mmol) in DMF (5 mL) was stirred at room temperature for 12 h. The reaction was concentrated *in vacuo*, and the crude product was purified by preparative thin layer chromatography (10:1:0.1 CH_2Cl_2: MeOH:$NH_3 \cdot H_2O$) to afford 90 mg of **1113** in a yield of 71%. MS (ESI): 424.0 (100%, $(M+H)^+$).

Example 29 – Synthesis of Isoxazole 2001

Scheme 22 depicts the reaction leading to isoxazole **2001**. Hydroxyisoxazole **201** was coupled to alcohol **51** using the Mitsunobu reaction to yield isoxazole **2001**.

Scheme 22



201 51 2001

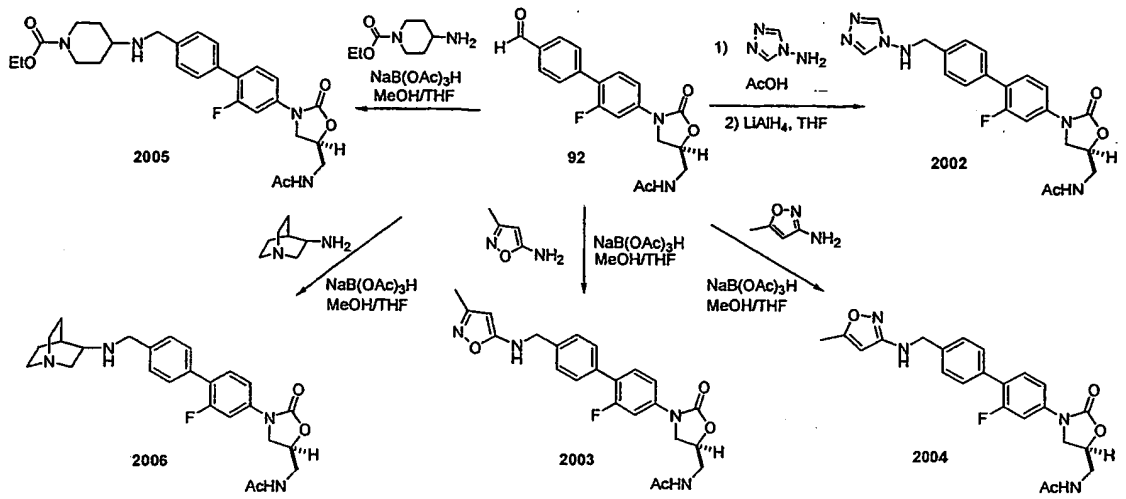
Synthesis of isoxazole 2001

The known isoxazole **201** was synthesized from methyl tetrolate as reported in literature (Iwai, I. *et al. Chem. Pharm. Bull.* **1966**, *14*, 1277-1286). To a suspension of isoxazole **201** (33 mg, 0.279 mmol), alcohol **51** (100 mg, 0.335 mmol) and triphenyl phosphine (95 mg, 0.363 mmol) was added diisopropyl azodicarboxylate (DIAD, 0.072 mL, 0.363 mmol) at -20°C. The reaction mixture was warmed to ambient temperature and stirred for 3 h. The solution was concentrated and purified by flash chromatography (4% MeOH in 1:1 CH_2Cl_2/EtOAc) to yield 64 mg of **2001**. LCMS (ESI) *m/z* 440 $(M + H)^+$.

Example 30 – Synthesis of Compounds 2002-2006

Scheme 23 illustrates the reductive amination chemistry leading to compounds **2002-2006**. Aldehyde **92** is treated with various amines in the presence of a reducing agent to yield the desired targets.

Scheme 23



Synthesis of triazole 2002

A suspension of the aldehyde **92** (178 mg, 0.5 mmol) in THF (4.0 mL) was treated with [1,2,4]triazol-4-ylamine (84 mg, 1.0 mmol) and acetic acid (0.02 mL) at room temperature, and the resulting reaction mixture was stirred at room temperature for 1 h before lithium aluminumhydride (38 mg, 1.0 mmol) was added at room temperature. The resulting reaction mixture was stirred at room temperature for an additional 1 h. When TLC and LCMS showed the reaction was complete, the reaction mixture was concentrated *in vacuo*, and the residue was directly purified by column chromatography (0–5% MeOH/CH_2Cl_2 gradient elution) to afford the desired triazole **2002** (40 mg; 19%) as a yellow solid. LCMS (ESI) *m/z* 425 $(M + H)^+$.

Synthesis of isoxazole 2003

A suspension of aldehyde **92** (107 mg, 0.3 mmol) in MeOH (4.0 mL) and THF (1.0 mL) was treated with 3-methyl-isoxazol-5-ylamine (59 mg, 0.6 mmol) and sodium triacetoxyborohydride (127 mg, 0.6 mmol) at 25°C, and the resulting reaction mixture was stirred at 25°C for 6 h. When TLC and LCMS showed the reductive amination reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford the desired

isoxazole **2003** (12 mg; 9% yield) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 439 $(M + H)^+$.

Synthesis of isoxazole 2004

A solution of aldehyde **92** (107 mg, 0.3 mmol) in MeOH (3.0 mL) and THF (3.0 mL) was treated with 5-methyl-isoxazol-3-ylamine (59 mg, 0.6 mmol) and sodium triacetoxyborohydride (127 mg, 0.6 mmol) at 25°C, and the resulting reaction mixture was stirred at 25°C for 6 h. When TLC and LCMS showed the reductive amination reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford isoxazole **2004** (41 mg; 31%) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 439 $(M + H)^+$.

Synthesis of carbamate 2005

A suspension of aldehyde **92** (142 mg, 0.4 mmol) in MeOH (4.0 mL) and THF (1.0 mL) was treated with 4-amino-piperidine-1-carboxylic acid ethyl ester (69 mg, 0.4 mmol) and sodium triacetoxyborohydride (160 mg, 0.8 mmol) at 25°C, and the resulting reaction mixture was stirred at 25°C for 6 h. When TLC and LCMS showed the reductive amination reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford carbamate **2005** (98 mg; 48% yield) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 513 $(M + H)^+$.

Synthesis of bicyclic diamine 2006

A suspension of aldehyde **92** (142 mg, 0.4 mmol) in MeOH (4.0 mL) and THF (1.0 mL) was treated with 1-aza-bicyclo[2.2.2]oct-3-ylamine (80 mg, 0.4 mmol) and sodium triacetoxyborohydride (160 mg, 0.8 mmol) at 25°C, and the resulting reaction mixture was stirred at 25°C for 6 h. When TLC and LCMS showed the reductive amination reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford diamine **2006** (71 mg; 38% yield) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 467 $(M + H)^+$.

Example 31 – Synthesis of Compounds 2007 and 2008

Synthesis of amide 2007

To a solution of anthranilamide (74 mg, 0.532 mmol) and mesylate **52** (100 mg, 0.229 mmol) in DMF (2.0 mL) was added Hunig's base (185 μL, 1.06 mmol). The mixture was stirred at 80°C for 16 h, then the mixture was concentrated by vacuum. The residue was directly isolated by reverse-phase preparative HPLC, to give 112 mg of **2007** as a white powder in 88% yield. LCMS (ESI) *m/z* 477 $(M + H)^+$.

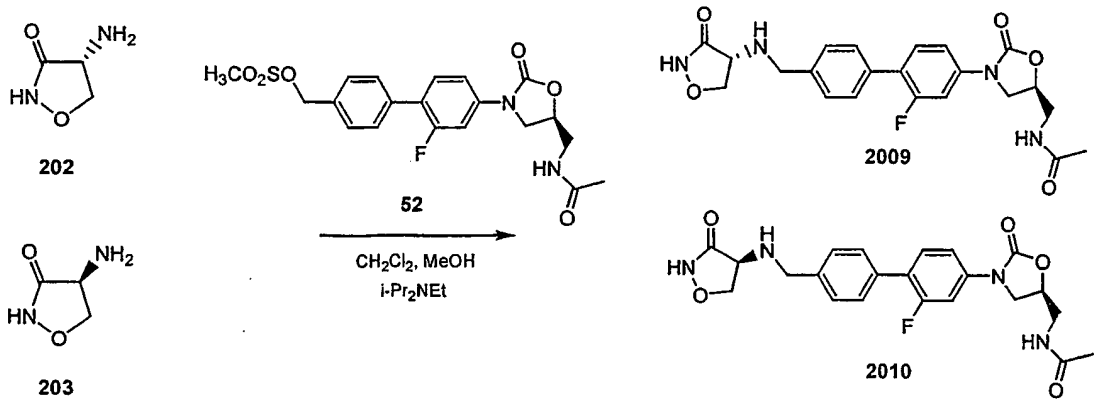
Synthesis of amide 2008

To a solution of 3-aminothiophene-2-carboxamide (67 mg, 0.459 mmol) and mesylate **52** (100 mg, 0.229 mmol) in DMF (2.0 mL) was added Hunig's base (160 μL, 0.916 mmol). The mixture was stirred at 80°C for 16 h, then the mixture was concentrated under vacuum. The residue was directly isolated by flash chromatography on silica gel (5:100 MeOH/CH_2Cl_2 as eluant), to afford 51 mg of **2008** as a white powder in 46% yield. LCMS (ESI) *m/z* 482 $(M + Na)^+$.

Example 32 – Synthesis of Compounds 2009 and 2010

Scheme 24 depicts the synthesis of **2009** and **2010** from D- and L-cycloserine respectively via alkylation with mesylate **52**.

Scheme 24



Synthesis of cycloserine derivative 2009

A mixture of D-cycloserine **202** (0.22 g, 2.04 mmol) and mesylate **52** (0.30 g, 0.68 mmol) in anhydrous CH_2Cl_2 (5 mL), MeOH (5 mL) and Hunig's base (2 mL) was heated to reflux for 3 h. The solvent was evaporated and the crude was purified on silica gel column,

eluting with CH_2Cl_2/MeOH 20:1 then with CH_2Cl_2/MeOH/NH_4OH 20:1:0.04 to 16:1:0.04 to give a white solid. The isolated solid was titurated with Et_2O/CH_3CN 1:1 (15 mL) and the suspension filtered to give analytically pure **2009** as a white solid (0.072 g, 24%). LCMS (ESI) *m/z* 443 $(M + H)^+$.

Synthesis of cycloserine derivative 2010

Compound **2010** was synthesized from L-cycloserine **203** and mesylate **52** as described above for the synthesis of **2009**. LCMS (ESI) *m/z* 443 $(M + H)^+$.

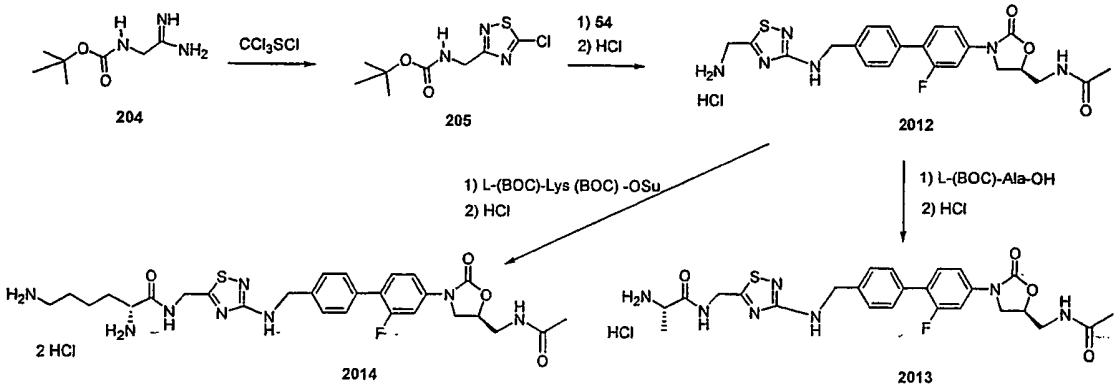
Example 33 – Synthesis of Azetidine 2011

A mixture of aldehyde **92** (100 mg, 0.28 mmol) and tert-butyl 3-amino-azetidine-1-carboxylate (58 mg, 0.34 mmol) in THF (2 mL) and DMF (0.5 mL) was stirred at room temperature for 1 h. Sodium triacetoxyborohydride (120 mg, 0.56 mmol) was added. After stirring at room temperature for 2 h, the reaction was concentrated, and the residue was dissolved in CH_2Cl_2, washed with water, and dried over $MgSO_4$. The CH_2Cl_2 solution was treated with trifluoroacetic acid (0.5 mL) at room temperature. After stirring for 1 h, the mixture was concentrated and purified by preparative thin layer chromatography (10:1:0.05 CH_2Cl_2/MeOH/$NH_3.H_2O$) to afford 45 mg of **2011** in a yield of 39%. LCMS (ESI) *m/z* 413.1 $(M + H)^+$.

Example 34 – Synthesis of Thiadiazoles 2012-2013

As Scheme 25 illustrates, thiadiazole **2012** was synthesized from chlorothiadiazole **205** by substitution with amine **54** followed by BOC deprotection. Acylation of **2012** with aminoacid fragments afforded thiadiazoles **2013** and **2014**.

Scheme 25



Synthesis of chlorothiadiazole 205

To a solution of BOC-aminoacetoamidine **204** (3.11 g, 18 mmol) in CH_2Cl_2 (60 mL) was added 3M NaOH (12.6 mL, 37.7 mmol) at -10°C. Under strong stirring, half of a solution of trichloromethanesulfenyl chloride (Cl_3CSCl, 1.96 mL, 18 mmol) in CH_2Cl_2 (30 mL) was slowly added. Then an additional 3M NaOH (12.6 mL, 37.7 mmol) was added, followed by the remaining Cl_3CSCl solution. The mixture was stirred at -10°C for 30 min and then at 0°C for 15 min before being diluted with ice-water (50 mL) and extracted with in CH_2Cl_2 (2 x 80 mL). The combined organic layer was washed with brine (1 x 20 mL), dried over Na_2SO_4 and the solvent was evaporated. The crude residue was purified on silica gel eluting with hexanes/ethyl acetate 6:1, yielding **205** as a yellow oil (2.9 g; 65%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.12 (s 1H), 4.42-4.40 (m, 2H), 1.29 (s, 9H).

Synthesis of thiadiazole 2012

To a solution of the amine **54** (1.0 g, 2.8 mmol) in MeOH (15 mL) and DMF (3 mL) was added chlorothiadiazole **205** (800 mg, 3.1 mmol) and Hunig's base (1 mL, 5.6 mmol). The mixture was stirred at 50°C overnight and then poured into 5% Na_2CO_3/ice (20 mL) and extracted with 9:1 CH_2Cl_2-isopropanol (2 x 100 mL). The combined organic layer was dried over Na_2SO_4 and the solvent evaporated. The crude residue was purified on silica gel eluting with 10:1 ethyl acetate/CH_2Cl followed by 95:5 ethyl acetate/MeOH, yielding white crystals, which were dissolved in 4M HCl in dioxane (20 mL). The mixture was stirred at room temperature for 2 h. The suspension was filtered and washed with ether (2 x 10 mL), and dried at high vacuum, yielding **2012** (830 mg; 93%). LCMS (ESI) *m/z* 471 $(M + H)^+$.

Synthesis of thiadiazole 2013

To a solution of thiadiazole **2012** (150 mg, 0.30 mmol) in CH_2Cl_2 (4 mL) and DMF (3 mL) was added Hunig's base (0.16 mL, 0.90 mmol), (L)-BOC-Ala-OH (67 mg, 0.36 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 79 mg, 0.42 mmol). The mixture was stirred overnight at room temperature, then additional amounts of (L)-BOC-Ala-OH (34 mg, 0.18 mmol), EDCI (40 mg, 0.21 mmol) and Hunig's base (0.08 mL, 0.44 mmol) were added. The mixture was stirred at room temperature overnight, poured into 1N HCl-ice (20 mL), and extracted with CH_2Cl_2-isopropanol 95:5 (2 x 50 mL). The combined organic layer was washed with water (15 mL), 5% sodium carbonate (Na_2CO_3, 15 mL), water (15 mL), brine (15 mL), and then dried over Na_2SO_4 and the solvent evaporated. The crude

residue was purified on silica gel eluting with ethyl acetate/ MeOH 95:5. The residue was dissolved in 4M HCl in dioxane (7 mL). The mixture was stirred at room temperature for 2 h and then evaporated. The residue was diluted with ether (3 mL), filtered, and the solid washed with ether (2 x 5 mL), then dried at high vacuum, yielding **2013** (122 mg; 91%). LCMS (ESI) *m/z* 542 $(M + H)^+$.

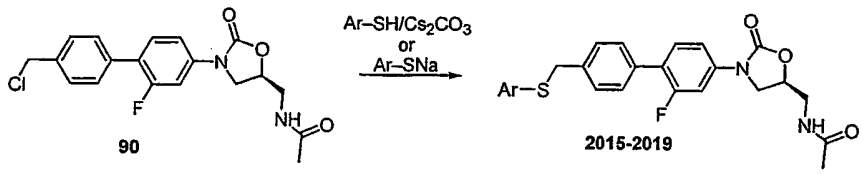
Synthesis of thiadiazole 2014

To a solution of of thiadiazole **2012** (150 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) and DMF (3 mL) was added Hunig's base (0.08 mL, 0.45 mmol) and (L)-BOC-Lys (BOC)-OSu (157 mg, 0.36 mmol). The mixture was stirred overnight at room temperature, poured into 5% Na_2CO_3-ice (20 mL), extracted with CH_2Cl_2-isopropanol 95:5 (3 x 50 mL), dried over Na_2SO_4 and the solvent evaporated. The crude residue was purified on silica gel eluting with ethyl acetate followed by 5:1 ethyl acetate / MeOH. The BOC-protected material obtained was dissolved in 4M HCl in dioxane (6 mL) and MeOH (2 mL), stirred at room temperature for 3 h and then evaporated. The residue was diluted with ether (6 mL), filtered, washed with ether (2x 5 mL) and dried at high vacuum, yielding **2014** (100 mg; 50%). LCMS (ESI) *m/z* 599 $(M + H)^+$.

Example 35 – Synthesis of Compounds 2015-2019

As Scheme 26 illustrates, benzyl chloride **90** served as alkylating agent for thiolates or thiols to afford compounds **2015-2019**.

Scheme 26



Synthesis of tetrazole 2015

A solution of chloride **90** (0.15 g, 0.40 mmol) in DMF (2 mL) was treated with 5-mercapto-4-methyltetrazole, sodium salt, dihydrate (0.14 g, 0.80 mmol) and stirred at 23°C for 0.5 h. The reaction mixture was diluted with water and the precipitate was recovered by vacuum filtration to afford tetrazole **2015** as a white powder (63%). LCMS (ESI) *m/z* 456 $(M + H)^+$.

Synthesis of triazole 2016

Tetrazole **2016** was prepared with chloride **90** (0.30 g, 0.80 mmol) and 4-mercapto-1,2,3-triazole, sodium salt, (0.20 g, 1.6 mmol) according to the procedure above used to synthesize tetrazole **2015** to afford **2016** as a yellow powder (0.29 g, 0.66 mmol, 82%). LCMS (ESI) *m/z* 442 $(M + Na)^+$.

Synthesis of compound 2017

Compound **2017** was prepared with chloride **90** (0.20 g, 0.53 mmol) and 2-thiobarbituric acid, sodium salt, (0.18 g, 1.1 mmol) according to the procedure above used to synthesize tetrazole **2015** to afford **2017** as a white powder (0.078 g, 0.16 mmol; 30%). LCMS (ESI) *m/z* 507 $(M + Na)^+$.

Synthesis of mercaptopyridine 2018

A solution of chloride **90** (0.20 g, 0.53 mmol) in DMF (2.7 mL) was treated with cesium carbonate (0.21 g, 0.64 mmol) and 2-mercaptopyridine (0.071 g, 0.64 mmol) and was stirred at 23°C for 0.5 h. The reaction mixture was diluted with water and the precipitate was recovered by vacuum filtration to afford **2018** as a yellow powder (91%). LCMS (ESI) *m/z* 452 $(M + H)^+$.

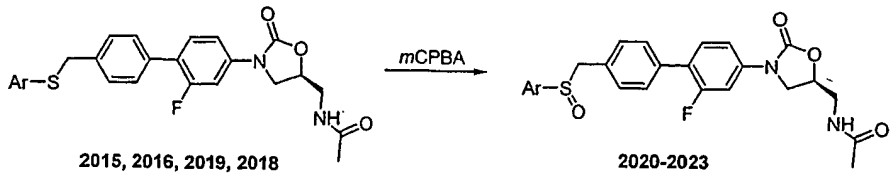
Synthesis of mercaptopyridine 2019

Mercaptopyridine **2019** was prepared with chloride **90** (0.20 g, 0.53 mmol), cesium carbonate (0.21 g, 0.64 mmol), and 4-mercaptopyridine (0.071 g, 0.64 mmol) according to the procedure above used to synthesize **2018** to afford a yellow powder (0.078 g, 0.16 mmol; 30%). LCMS (ESI) *m/z* 452 $(M + H)^+$.

Example 36 – Synthesis of Sulfoxides 2020-2023

As Scheme 27 illustrates, sulfides **2015**, **2016**, **2019**, and **2018** were oxidized under controlled conditions to afford sulfoxides **2020-2023** respectively.

Scheme 27



2015, 2016, 2019, 2018 2020-2023

Synthesis of sulfoxide 2020

A solution of **2015** (0.020 g, 0.044 mmol) in chloroform (0.44 mL) and methanol (0.050 mL) was treated with 3-chloroperoxybenzoic acid (77%, 0.010 g, 0.044 mmol) and stirred at 23°C for 12 h. The reaction mixture was diluted with methylene chloride, washed with saturated aqueous sodium bicarbonate, dried over Na_2SO_4, and the solvent removed *in vacuo*. The crude product was purified with preparative TLC (1:4.5:4.5 MeOH/ethyl acetate/CH_2Cl_2) to afford **2020** as a white powder (3.6 mg, 0.008 mmol; 19%). LCMS (ESI) *m/z* 495 $(M + Na)^+$.

Synthesis of sulfoxide 2021

Sulfoxide **2021** was prepared from sulfide **2016** (0.030 g, 0.068 mmol) and 3-chloroperoxybenzoic acid (77%, 0.015 g, 0.068 mmol) according to the procedure described above for the synthesis of sulfoxide **2020** to afford a white powder (0.021 g, 0.046 mmol; 68%). LCMS (ESI) *m/z* 480 $(M + Na)^+$.

Synthesis of sulfoxide 2022

Sulfoxide **2022** was prepared from sulfide **2019** (0.080 g, 0.18 mmol) and 3-chloroperoxybenzoic acid (77%, 0.040 g, 0.18 mmol) according to the procedure described above for the synthesis of sulfoxide **2020** to afford a white powder (0.021 g, 0.094 mmol; 52%). LCMS (ESI) *m/z* 468 $(M + H)^+$.

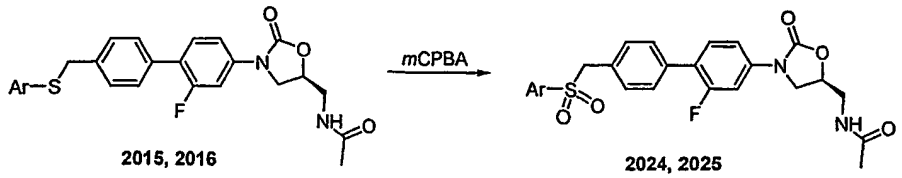
Synthesis of sulfoxide 2023

Sulfoxide **2023** was prepared from sulfide **2018** (0.10 g, 0.22 mmol) and 3-chloroperoxybenzoic acid (77%, 0.050 g, 0.22 mmol) according to the procedure described above for the synthesis of sulfoxide **2020** to afford a white powder (0.068 g, 0.15 mmol; 66%). LCMS (ESI) *m/z* 466.

Example 37 – Synthesis of Sulfones 2024 and 2025

As Scheme 28 illustrates, sulfides **2015** and **2016** were oxidized with excess 3-chloroperoxybenzoic acid to afford sulfones **2024** and **2025**.

Scheme 28



2015, 2016 2024, 2025

Synthesis of sulfone 2024

A solution of sulfide **2015** (0.020 g, 0.044 mmol) in chloroform (0.44 mL) and methanol (0.050 mL) was treated with 3-chloroperoxybenzoic acid (77%, 0.030 g, 0.13 mmol) and stirred at 23°C for 1 h and then heated to 50°C for 12 h. The reaction mixture was cooled to 23°C, diluted with methylene chloride, washed with saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and the solvent removed *in vacuo*. The crude product was purified by preparative TLC (5% MeOH in CH_2Cl_2) to afford sulfone **2024** as a white powder (3.6 mg; 17%). LCMS (ESI) *m/z* 489 $(M + H)^+$.

Synthesis of sulfone 2025

A solution of sulfide **2016** (0.050 g, 0.11 mmol) in chloroform (1.1 mL) and methanol (0.1 mL) was treated with 3-chloroperoxybenzoic acid (77%, 0.076 g, 0.34 mmol) and stirred at 23°C for 2 h. The precipitate was recovered through vacuum filtration to yield sulfone **2025** as a white solid (0.020 g; 37%). LCMS (ESI) *m/z* 474 $(M + H)^+$.

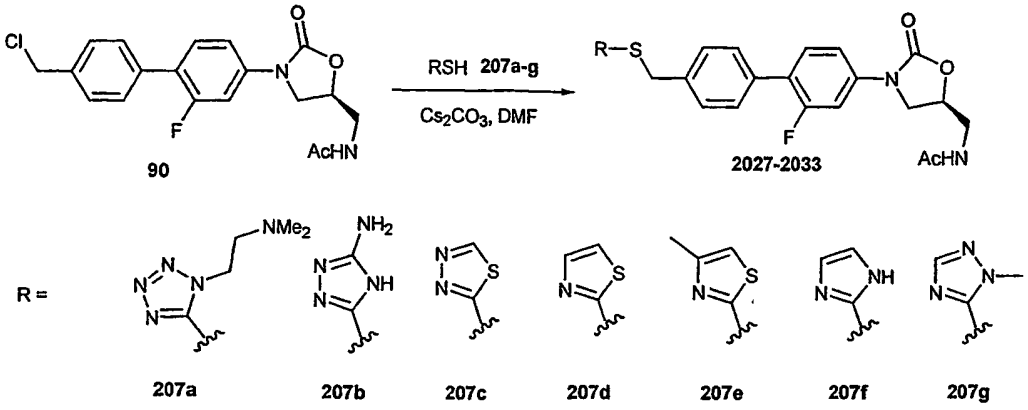
Example 38 – Synthesis of Mercaptotriazole 2026

A solution of mesylate **64** (0.012 g, 0.027 mmol) in DMF (0.14 mL) was treated with 4-mercapto-1,2,3-triazole, sodium salt (7 mg, 0.054 mmol) and was stirred at 45°C for 2 h. The solvent was removed *in vacuo* and the crude product was purified by preparative TLC (5% MeOH in CH_2Cl_2) to afford mercaptotriazole **2026** as a white solid (3.1 mg; 24%). LCMS (ESI) *m/z* 456 $(M + H)^+$.

Example 39 – Synthesis of Compounds 2027-2033

As Scheme 29 illustrates, benzyl chloride **90** was used to alkylate thiols **207a-g** to provide compounds **2027-2033** respectively.

Scheme 29



Synthesis of tetrazole 2027

Benzyl chloride **90** (0.20 g, 0.53 mmol) was dissolved in DMF (5 mL). Thiol **207a** (62 mg, 0.53 mmol) and cesium carbonate (0.20 g, 0.64 mmol) were added sequentially and the resulting slurry stirred at room temperature for 4 h. The mixture was poured into 70 mL H_2O and stirred for 1 h. The solids were filtered, rinsed with ether and dried under vacuum to afford tetrazole **2027** as a brown solid (187 mg, 0.36 mmol). LCMS (ESI) *m/z* 514 $(M + H)^+$.

Synthesis of triazole 2028

Triazole **2028** was synthesized by the process described for **2027** above using thiol **207b** in place of **207a** to yield 138 mg of triazole **2028** as a yellow solid (0.30 mmol). LCMS (ESI) *m/z* 457 $(M + H)^+$.

Synthesis of thiadiazole 2029

Thiadiazole **2029** was synthesized by the process described for **2027** above using thiol **207c** in place of **207a** to yield 147 mg of thiadiazole **2029** as a white solid (0.32 mmol). LCMS (ESI) *m/z* 481 $(M + Na)^+$, 522 $(M + Na + CH_3CN)^+$.

Synthesis of thiazole 2030

Thiazole **2030** was synthesized by the process described for **2027** above using thiol **207d** in place of **207a** to yield 129 mg of thiazole **2030** as a white solid (0.28 mmol). LCMS (ESI) *m/z* 458 $(M + H)^+$, 521 $(M + Na + CH_3CN)^+$.

Synthesis of thiazole 2031

Thiazole **2031** was synthesized by the process described for **2027** above using thiol **207e** in place of **207a** to yield 155 mg of thiazole **2031** as an off-white solid (0.33 mmol). LCMS (ESI) *m/z* 472 $(M + H)^+$.

Synthesis of imidazole 2032

Imidazole **2032** was synthesized by the process described for **2027** above using thiol **207f** in place of **207a** to yield 91 mg of imidazole **2032** as a white solid (0.21 mmol). LCMS (ESI) *m/z* 441 $(M + H)^+$.

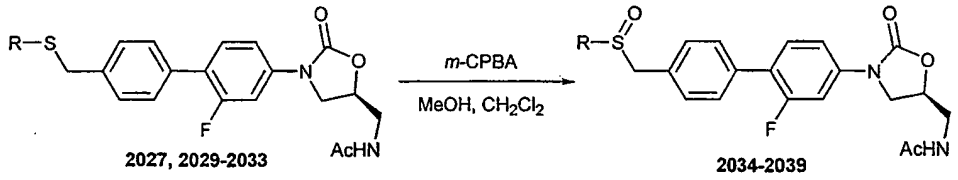
Synthesis of triazole 2033

Triazole **2033** was synthesized by the process described for **2027** above using thiol **207g** in place of **207a** to yield 91 mg of triazole **2033** as a white solid (0.21 mmol). LCMS (ESI) *m/z* 456 $(M + H)^+$, 478 $(M + Na)^+$, 519 $(M + Na + CH_3CN)^+$.

Example 40 – Synthesis of Compounds 2034-2039

As Scheme 30 illustrates, compounds **2027** and **2029-2033** were oxidized to afford sulfoxides **2034-2039** respectively.

Scheme 30



2027, 2029-2033 2034-2039

Synthesis of sulfoxide 2034

Tetrazole **2027** (80 mg, 0.16 mmol) was dissolved in 3:1 CH_2Cl_2/MeOH (3 mL). *m*-CPBA was added (75% pure; 39 mg, 0.17 mmol) and the mixture was stirred at room temperature for 6 h. The reaction mixture was poured into 50 mL ether and stirred for 1 h. The solids were filtered and dried *in vacuo* to give sulfoxide **2034** as an off-white solid (55 mg, 0.10 mmol). LCMS (ESI) *m/z* 530 $(M + H)^+$.

Synthesis of sulfoxide 2035

Sulfoxide **2035** was synthesized by the process described above for **2034** starting with thiadiazole **2029** in place of tetrazole **2027** to yield 39 mg of **2035** as a white solid (0.08 mmol). LCMS (ESI) *m/z* 497 $(M + Na)^+$, 538 $(M + Na + CH_3CN)^+$.

Synthesis of sulfoxide 2036

Sulfoxide **2036** was synthesized by the process described above for **2034** starting with thiazole **2030** in place of tetrazole **2027** to yield 48 mg of **2036** as an off-white solid (0.10 mmol). LCMS (ESI) *m/z* 496 $(M + Na)^+$, 537 $(M + Na + CH_3CN)^+$.

Synthesis of sulfoxide 2037

Sulfoxide **2037** was synthesized by the process described above for **2034** starting with thiazole **2031** in place of tetrazole **2027** to yield 44 mg of **2037** as an off-white solid (0.09 mmol). LCMS (ESI) *m/z* 488 $(M + H)^+$, 510 $(M + Na)^+$, 551 $(M + Na + CH_3CN)^+$.

Synthesis of sulfoxide 2038

Sulfoxide **2038** was synthesized by the process described above for **2034** starting with imidazole **2032** in place of tetrazole **2027** to yield 51 mg of **2038** as a white solid (0.11 mmol). LCMS (ESI) *m/z* 457 $(M + H)^+$.

Synthesis of sulfoxide 2039

Sulfoxide **2039** was synthesized by the process described above for **2034** starting with triazole **2033** in place of tetrazole **2027** to yield 48 mg of **2039** as a white solid (0.10 mmol). LCMS (ESI) *m/z* 472 $(M + H)^+$ 494 $(M + Na)^+$, 535 $(M + Na + CH_3CN)^+$.

Example 41 – Synthesis of Compound 2040

A solution of mesylate **106** (43.7 mg, 1.0 mmol) in anhydrous DMF (4.0 mL) was treated with 1*H*-5-mercapto-1,2,3-triazole sodium salt (24.6 mg, 2.0 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature overnight. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*, and the residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford mercaptotriazole **2040** (29.0 mg; 66%) as a pale-yellow solid. LCMS (ESI) *m/z* 443 $(M + H)^+$.

Example 42 – Synthesis of Compounds 2043 and 2044

Synthesis of compound 2043

A solution of amine **54** (0.070 g, 0.20 mmol) in DMF (1.0 mL) was treated with triethylamine (0.055 mL, 0.40 mmol) and 1-methyl-1H-imidazole-4-sulfonyl chloride (0.039 mg, 0.22 mmol) and stirred at 23 °C for 30 minutes. The solvent was removed *in vacuo*, and

the crude product was purified by flash chromatography (4.5:4.5:1 methylene chloride/ethyl acetate/methanol) to afford compound **2043** (0.054 g, 0.11 mmol, 55%). MS (ESI): 502 $(M+H)^+$.

Synthesis of Compound 2044

A solution of amine **54** (0.070 g, 0.20 mmol) in DMF (1.0 mL) was treated with triethylamine (0.055 mL, 0.40 mmol) and 6-morpholin-4-yl-pyridine-3-sulfonyl chloride (0.057 g, 0.22 mmol) and stirred at 23 °C for 30 minutes. The solvent was removed *in vacuo*, and the crude product was purified by flash chromatography (0-10% methanol in 1:1 ethyl acetate/ methylene chloride) to afford compound **2044** (0.052 g, 0.09 mmol, 45%). MS (ESI): 584 $(M+H)^+$.

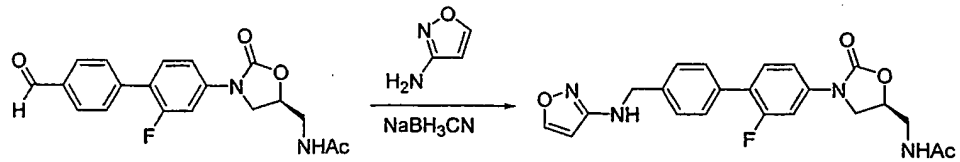
Example 43 – Synthesis of Compound 2047

A solution of chloride **90** (0.19 g, 0.50 mmol) in DMF (5 mL) was treated with 3-mercapto-1,2,4-triazole (0.20 g, 1.0 mmol) and Cs_2CO_3 (0.33 g, 1.0 mmol), and stirred at 23 °C for 1 h. The reaction mixture was diluted with H_2O (45 mL), and the resulting precipitate filtered, washed with H_2O and dried under vacuum to afford compound **2047** (0.139 g, 0.315 mmol, 63%) as a white powder. MS (ESI): 442 $(M+H)^+$.

Example 44 – Synthesis of Compound 2050

Scheme 31 depicts the synthesis of compound **2050**.

Scheme 31

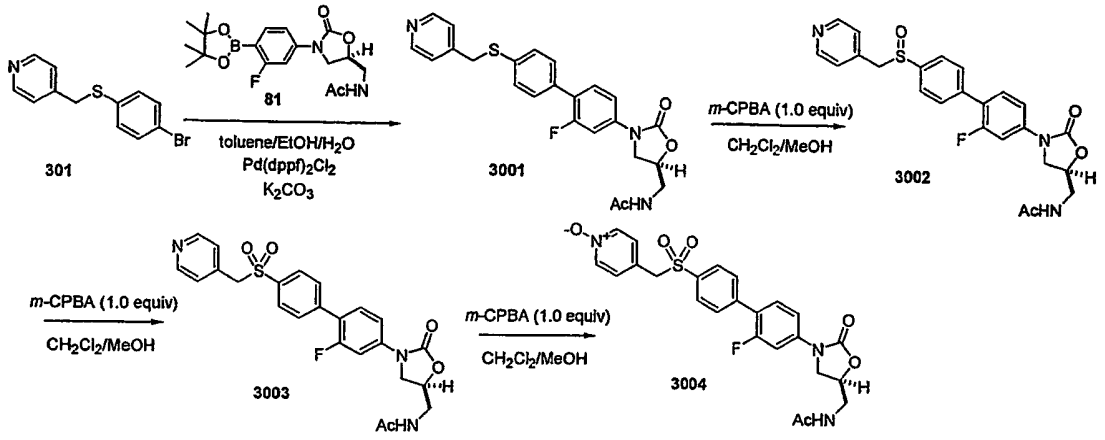


To a solution of 0.050 g (0.15 mmol) of aldehyde **92** and 0.026 g (0.30 mmol) of aminoisoxazole in 2 ml of TFA at 25 °C was added 0.018 g (0.30 mmol) of sodium cyanoborohydride ($NaBH_3CN$). The reaction mixture was stirred at 25 °C for 4 h. The TFA was removed, and the residue was purified by preparative TLC to give 0.040 g of compound **2050**. MS (M+1): 425.

Example 45 – Synthesis of Compounds 3001-3004

As Scheme 32 illustrates, bromide **301** was coupled to boronate **81** to yield pyridyl derivative **3001**. Successive oxidations provided sulfoxide **3002**, sulfone **3003**, and the pyridyl *N*-oxide **3004**.

Scheme 32



Synthesis of bromide 301

A suspension of 4-bromomethylpyridine hydrochloride (1.59 g, 6.3 mmol) in THF (10 mL) was treated dropwise with a solution of potassium carbonate (3.33 g, 24.0 mmol) in H_2O (6 mL) at 0–5°C, and the resulting mixture was stirred at 0–5°C for 10 min before being treated dropwise with a solution of 4-bromo-benzenethiol (1.14 g, 6.0 mmol) in THF (5.0 mL) at 0–5°C under N_2. The resulting reaction mixture was subsequently stirred at 0–5°C for an additional 20 min. When TLC and LCMS showed that the reaction was complete, the reaction mixture was treated with water (15 mL) and ethyl acetate (25 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with water (2 x 15 mL) and saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (5–25% EtOAc-hexane gradient elution) to afford the desired 4-(4-bromo-phenylsulfanylmethyl) pyridine **301** (1.374 g; 82%) as a pale-yellow solid, which was directly used in subsequent reactions.

Synthesis of compound 3001

A solution of boronate **81** (200 mg, 0.53 mmol) and bromide **301** (150 mg, 0.53 mmol) in toluene (9 mL) was treated with solid potassium carbonate (220 mg, 1.6 mmol), ethanol (3.0

mL) and H_2O (3.0 mL) at room temperature, and the resulting reaction mixture was degassed three times under a steady stream of argon before being treated with $Pd(dppf)_2Cl_2$ (16 mg, 0.013 mmol) at room temperature. The reaction mixture was then degassed three times again under a steady stream of argon before being warmed up to reflux for 2 h. When LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature before being treated with water (10 mL) and ethyl acetate (20 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with water (2 x 10 mL) and saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford compound **3001** (177 mg; 74%) as a yellow oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 452 $(M + H)^+$.

Synthesis of sulfoxide 3002

A solution of compound **3001** (58 mg, 0.13 mmol) in CH_2Cl_2 (2.0 mL) and MeOH (0.5 mL) was treated with *m*-CPBA (22 mg, 0.13 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 2 h. The solvents were removed, and the residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford sulfoxide **3002** (43 mg; 71%) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 468 $(M + H)^+$.

Synthesis of sulfone 3003

A solution of sulfoxide 2002 (22 mg, 0.047 mmol) in CH_2Cl_2 (2.0 mL) and MeOH (0.5 mL) was treated with *m*-CPBA (9.0 mg, 0.047 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 2 h. The solvents were removed, and the residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford sulfone **3003** (16 mg; 71%) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 484 $(M + H)^+$.

Synthesis of pyridyl *N*-oxide 3004

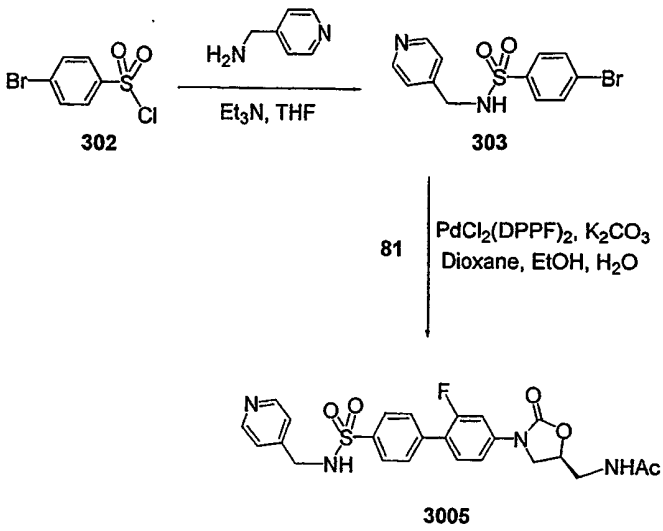
A solution of sulfone **3003** (16 mg, 0.033 mmol) in CH_2Cl_2 (1.0 mL) and MeOH (0.5 mL) was treated with *m*-CPBA (6.0 mg, 0.033 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 2 h. The solvents were removed, and the residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient

elution) to afford the pyridyl *N*-oxide **3004** (11 mg; 67% yield) as colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 500 $(M + H)^+$.

Example 46 – Synthesis of Compound 3005

Scheme 33 illustrates the synthesis of compound **3005.**

Scheme 33



Synthesis of bromide 303

4-bromobenzenesulfonyl chloride **302** (2.56 g, 10 mmol) was added to a solution of 4-aminomethylpyridine (1.08 g, 10 mmol) and triethylamine (2 mL, 14.3 mmol) in THF (20 mL) at 0 °C. After stirring at same temperature for 1 h, 50 mL of cool water was added. A white solid was collected by filtration, washing with EtOAc and dried in vaccum to give 3.10 g of bromide **303** in a yield of 95%.

Synthesis of compound 3005

Bromide **303** (327 mg, 1 mmol), boronate **81** (378 mg, 1 mmol), $Pd(dppf)_2Cl_2$ (40 mg, 0.05 mmol) and K_2CO_3 (414 mg, 3 mmol) were dissolved 8 mL of a mixture of dioxane:EtOH: H_2O (3:1:1) under argon atmosphere. After heating at 100°C for 12 hours, the reaction was added to 20 mL of cool water. The organic solvent was removed *in vacuo* and the crude product was collected by filtration. The crude product was treated with active charcoal and recrystallized in a mixed solvent system (1:2:2 MeOH:CH_2Cl_2:acetone) to give 155 mg of **3005** in a yield of 31%. MS (ESI): 499.1 (100%, $(M+H)^+$).

Example 47 - Synthesis of Amide 4008

A solution of amine **54** (36 mg, 0.1 mmol) in DMF was treated with quinoline-4-carboxylic acid (26 mg, 0.15 mmol, 1.5 equiv) at 25 °C under N_2, and the resulting mixture was treated with EDCI (28.5 mg, 0.15 mmol, 1.5 equiv) at 25 °C under N_2. The reaction mixture was subsequently stirred at 25 °C for 12 h. When TLC and HPLC showed the coupling reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was then directly purified by flash column chromatography (0–7% MeOH-CH_2Cl_2 gradient elution) to afford the desired amide **4008** (36.4 mg, 71% yield) as an off-white powder. LCMS (ESI) *m/e* 513 ($M^+ + H$).

Example 48 – General Synthesis of Carboxylic Acid-Loaded Tfp Resins and Synthesis of Amide 4011

A suspension of polymeric 4-hydroxy-2,3,5,6-tetrafluorophenol (TFP, *J. Comb. Chem.* **2000**, *2*, 691) amide resin (1.00 g, 1.27 mmol) in DMF (10 mL) was shaken for 10 minutes in a 70 mL polypropylene cartridge and then treated with indole-6-carboxylic acid (1.02 g, 6.35 mmol), 3-hydroxybenzotriazole (18 mg, 0.13 mmol), and diisopropylcarbodiimide (1.2 mL, 7.6 mmol). The reaction mixture was shaken for 18 h at 23 °C, and then the resin was washed with DMF (10 x 50 mL), THF (10 x 50 mL), and methylene chloride (10 x 50 mL) and dried *in vacuo*.

A suspension of the above TFP ester (35 mg) in 1 mL of DMF was treated with amine **54** (10 mg, 0.027 mmol) and shaken for 18 h in a 10 mL polypropylene cartridge. The filtrate was collected and dried to give amide **4011** (11 mg, 0.022 mmol, 81%) as a yellow solid. ^{1}HNMR (300 MHz, 10:1 $CDCl_3$: CD_3OD): δ 7.89 (s, 1H), 7.75-7.71 (m, 1H), 7.55-7.52 (m, 1H), 7.46-7.30 (m, 6H), 7.16 (dd, J = 8, 2 Hz, 1H), 6.45-6.44 (m, 1H), 4.70-4.68 (m, 1H), 4.60-4.59 (m, 2H), 4.03-3.97 (m, 1H), 3.73-3.71 (m, 4H), 3.58-3.42 (m, 2H), 3.27-3.25 (m, 1H), 1.90 (s, 3H). LCMS (ESI) *m/e* 501.0 $(M+H)^+$.

Example 49 – Synthesis of Amides 4010 and 4012-4105

Synthesis of Amide 4010

Amide **4010** was prepared from the TFP ester of *N*-methylpyrrole-2-carboxylic acid (477 mg, 3.81 mmol), which was prepared according to the general method of Example 48. The TFP ester was reacted with amine **54** using the acylation procedure of Example 48 to synthesize amide **4011**. The desired amide **4010** was obtained as a solid (10 mg, 0.022 mmol,

81%). ^{1}HNMR (300 MHz, 10:1 $CDCl_3$: CD_3OD): δ 7.71-7.56 (m, 6H), 7.33 (dd, J = 9, 2 Hz, 1H), 6.93-6.92 (m, 1H), 6.77 (dd, J = 4, 2 Hz, 1H), 6.55 (dd, J = 12, 6 Hz, 2H), 6.27 (dd, J = 4, 3 Hz, 1H), 4.77-4.69 (m, 1H), 4.54-4.52 (m, 2H), 4.02-3.96 (m, 1H), 3.90 (s, 3H), 3.73 (dd, J = 9, 7 Hz, 1H), 3.62-3.58 (m, 2H), 1.96 (s, 3H). LCMS (ESI) *m/e* 465.0 $(M+H)^+$.

Synthesis of Amide 4012

Amide **4012** was prepared from the TFP ester of 3-methylsulfonylbenzoic acid (1.27 g, 6.35 mmol), which was prepared according to the general method of Example 48. The TFP ester was reacted with amine **54** using the acylation procedure of Example 48 to synthesize amide **4011**. The desired amide **4012** was obtained as a solid (13 mg, 0.024 mmol, 89%). ^{1}HNMR (300 MHz, 10:1 $CDCl_3$: CD_3OD): δ 8.31-8.30 (m, 1H), 8.14-8.11 (m, 1H), 8.00-7.97 (m, 1H), 7.64-7.58 (m, 2H), 7.45-7.29 (m, 6H), 7.12 (dd, J = 9, 2 Hz, 1H), 4.73-4.71 (m, 1H), 4.59-4.58 (m, 2H), 4.05-3.99 (m, 1H), 3.73 (dd, J = 9, 7 Hz, 1H), 3.61-3.44 (m, 6H), 3.30-3.27 (m, 1H), 3.03 (s, 3H). LCMS (ESI) *m/e* 540.1 $(M+H)^+$.

Synthesis of Amide 4013

Amide **4013** was prepared from the TFP ester of 4-fluorobenzoic acid (890 mg, 6.35 mmol), which was prepared according to the general method of Example 48. The TFP ester was reacted with amine **54** using the acylation procedure of Example 48 to synthesize amide **4011**. The desired amide **4013** was obtained as a solid (12 mg, 0.025 mmol, 93%). LCMS (ESI) *m/e* 480.0 $(M+H)^+$.

Synthesis of Amide 4014

Amide **4014** was prepared from the TFP ester of piperonylic acid (1.05 g, 6.35 mmol), which was prepared according to the general method of Example 48. The TFP ester was reacted with amine **54** using the acylation procedure of Example 48 to synthesize amide **4011**. The desired amide **4014** was obtained as a solid (13 mg, 0.026 mmol, 96%). ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.72-7.70 (m, 1H), 7.54-7.28 (m, 8H), 7.24-7.23 (m, 1H), 7.17 (dd, J = 9, 2 Hz, 1H), 5.93 (s, 2H), 4.65-4.79 (m, 1H), 4.54-4.52 (m, 2H), 4.05-3.99 (m, 1H), 3.72 (dd, J = 9, 7 Hz, 1H), 3.55-3.48 (m, 2H), 3.28-3.26 (m, 2H), 1.92 (s, 3H). LCMS (ESI) *m/e* 506.0 $(M+H)^+$.

Synthesis of Amide 4015

Amide **4015** was prepared from the TFP ester of 5-methoxyindole-2-carboxylic acid (486 mg, 2.54 mmol), which was prepared according to the general method of Example 48.

The TFP ester was reacted with amine **54** using the acylation procedure of Example 48 to synthesize amide **4011**. The desired amide **4015** was obtained as a solid (10 mg, 0.019 mmol, 70%). ^{1}HNMR (300 MHz, 10:1 $CDCl_3$: CD_3OD): δ 7.87-7.79 (m, 1H), 7.48-7.14 (m, 7H), 6.94 (s, 1H), 6.89-6.81 (m, 2H), 4.67-4.61 (m, 1H), 4.54-4.52 (m, 2H), 4.02-3.93 (m, 2H), 3.71-3.61 (s, 3H), 1.89 (s, 3H). LCMS (ESI) *m/e* 531.1 $(M+H)^+$.

Example 50 - Synthesis of Amine 4016

A solution of amine **54** (36 mg, 0.1 mmol) in a mixture of THF and DMF (3:1, v/v) was treated with quinoline-4-carboxaldehyde (16 mg, 0.1 mmol, 1.0 equiv) at 25 °C under argon, and the resulting reaction mixture was stirred at 25 °C for 30 min before being treated with sodium triacetoxyborohydride ($NaB(OAc)_3H$, 33 mg, 0.15 mmol, 1.5 equiv) at 25 °C. The reaction mixture was subsequently stirred at 25 °C for 6 h. When TLC and HPLC showed the reductive amination reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was then directly purified by flash column chromatography (0–7% MeOH-CH_2Cl_2 gradient elution) to produce the desired *N*-[3-(2-fluoro-4'-{[(quinolin-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide **4016** (32.9 mg, 66% yield) as pale-yellow oil, which solidified upon standing at room temperature *in vacuo*. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85 (s, 3H, $COCH_3$), 3.44 (t, 2H, J = 5.4 Hz), 3.79 (dd, 1H, J = 6.4, 9.2 Hz), 3.88 (s, 2H), 4.17 (t, 1H, J = 9.1 Hz), 4.30 (s, 2H), 4.77 (m, 1H), 7.41 (dd, 1H, J = 2.0, 8.0 Hz), 7.51–7.63 (m, 8H, aromatic-*H*), 7.74 (t, 1H, J = 8.0 Hz), 8.04 (d, 1H, J = 8.0 Hz), 8.18 (d, 1H, J = 8.0 Hz), 8.27 (t, 1H, J = 5.8 Hz, $NHCOCH_3$), 8.87 (d, 1H, J = 8.0 Hz). LCMS (ESI) *m/e* 499 $(M + H)^+$.

Example 51 - Synthesis of Amines 4018-4026

Synthesis of Amine 4018

To a solution of 0.032 g (0.089 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.009 g (0.080 mmol) of 4-pyridylcarboxaldehyde and 0.027 g (0.12 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction were removed via rotary evaporation and the residue was then purified on a preparative TLC plate to give 7.0 mg of **4018**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.57 (s, 1 H), 8.48 (d, J = 4.2 Hz, 1 H), 7.91-7.33 (a series of multiplet peaks, 9 H), 2.05 (s, 3 H). LCMS (ESI) *m/e* 449 $(M+H)^+$.

Synthesis of Amine 4019

To a solution of 0.080 g (0.22 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.032 g (0.20 mmol) of 2-quinolinecarboxaldehyde and 0.094 g (0.44 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction were removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 44 mg of **4019**. ^{1}H NMR (300 MHz, $CD_3OD + CDCl_3$): δ 8.32 (d, J = 5.4 Hz, 1 H), 8.06 (d, J = 5.4 Hz, 1 H), 7.94 (d, J = 6 Hz, 1 H), 7.79-7.36 (a series of multiplet peaks, 10 H), 4.83 (m, 1 H), 3.97 (s, 1 H), 2.05 (s, 3 H). LCMS (ESI) *m/e* 499 $(M+H)^+$.

Synthesis of 4020

To a solution of 0.080 g (0.22 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) was added 0.030 g (0.20 mmol) of 2-benzofurancarboxaldehyde and 0.094 g (0.44 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction were removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 49 mg of **4020**. ^{1}H NMR (300 MHz, $CD_3OD + CDCl_3$): δ 7.44-7.01 (a series of multiplet peaks, 11 H), 6.62 (s, 1 H), 3.92 (s, 2 H), 3.82 (s, 2 H), 3.75-3.60 (m, 1 H). LCMS (ESI) *m/e* 488 $(M+H)^+$.

Synthesis of Amine 4021

To a solution of 0.080 g (0.22 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.032 g (0.20 mmol) of 3-quinolinecarboxaldehyde and 0.094 g (0.44 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction was removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 49 mg of **4021**. ^{1}H NMR (300 MHz, $CD_3OD + CDCl_3$): δ 8.89 (s, 1 H), 8.33 (s, 1 H), 8.03 (d, J = 5.4 Hz, 1 H), 7.95 (d, J = 5.4 Hz, 1 H), 7.80 ~ 7.34 (a series of multiple peaks, 9 H), 1.98 (s, 3 H). LCMS (ESI) *m/e* 499 $(M+H)^+$.

Synthesis of Amine 4022

To a solution of 0.100 g (0.28 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.042 g (0.27 mmol) of 1-naphthaldehyde and 0.119 g (0.56 mmol) of

sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction were removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 49 mg of **4022**. ^{1}H NMR (300 MHz, CD_3OD + $CDCl_3$): δ 7.98 ~ 7.24 (a series of multiple peaks, 14 H), 2.00 (s, 3 H). LCMS (ESI) *m/e* 498 $(M+H)^+$.

Synthesis of Amine 4023

To a solution of 0.100 g (0.28 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.024 g (0.25 mmol) of 3-furaldehyde and 0.119 g (0.56 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction were removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 32 mg of 4023. ^{1}H NMR (300 MHz, CD_3OD + $CDCl_3$): δ 7.50 ~ 7.22 (a series of multiple peaks, 9 H), 6.39 (s, 1 H), 1.90 (s, 3 H). LCMS (ESI) *m/e* 438 $(M+H)^+$.

Synthesis of Amine 4024

To a solution of 0.100 g (0.28 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.027 g (0.25 mmol) of 2-pyridylcarboxaldehyde and 0.089 g (0.42 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction was removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 30.0 mg of **4024**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.39 (s, 1 H), 8.30 (d, J = 2.1 Hz, 1 H), 7.70 ~ 7.21 (a series of multiplet peaks, 9 H), 1.86 (s, 3 H). LCMS (ESI) *m/e* 449 $(M+H)^+$.

Synthesis of Amine 4025

To a solution of 0.100 g (0.28 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.027 g (0.25 mmol) of 3-pyridylcarboxaldehyde and 0.089 g (0.42 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction were removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 30.0 mg of **4025**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.57 (s, 1 H), 8.48 (d, J = 4.2 Hz, 1 H), 7.91 ~ 7.33 (a series of multiplet peaks, 9 H), 2.05 (s, 3 H). LCMS (ESI) *m/e* 449 $(M+H)^+$.

Synthesis of Amine 4026

To a solution of 0.100 g (0.28 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.024 g (0.25 mmol) of 2-furaldehyde and 0.089 g (0.42 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction were removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 26.6 mg of **4026**. ^{1}H NMR (300 MHz, CD_3OD): δ 7.52 ~ 7.26 (a series of multiplet peaks, 10 H), 1.87 (s, 3 H). LCMS (ESI) *m/e* 438 $(M+H)^+$.

Example 52 - Synthesis of Amine 4038

Method A

A solution of 8.00 g (115.9 mmol) of isoxazole and 31.30 g (139.1 mmol) of *N*-iodosuccinimide in 60 ml of trifluoroacetic acid was heated to 50°C for 6 h. The reaction mixture was cooled and evaporated at 0°C to remove the majority of trifluoroacetic acid. The residue was then dissolved in 200 ml of diethyl ether, washed sequentially with saturated $NaHCO_3$ (40 ml x 4), 10% sodium thiosulfate (40 ml x 2), and brine (40 ml), dried over $MgSO_4$, filtered and concentrated to give 16.50 g of the desired 4-iodoisoxazole product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (s, 1 H), 8.29 (s, 1 H).

To a solution of 6.80 g (34.8 mmol) of 4-iodoisoxazole in 200 ml of THF at -100°C was added dropwise 22.9 ml (36.6 mmol) of *n*-BuLi (1.6 M in hexanes). The reaction mixture was allowed to stir for 30 min. Ethyl formate (3.08 ml, 38.4 mmol) was added to the mixture, and the mixture was stirred further for 30 min at -100 °C. Hydrochloric acid (36.60 ml of 1 *N* HCl in ether) was added at -100 °C, and the reaction mixture was allowed to warm gradually to 25°C. The mixture was diluted with ether (200 ml), washed sequentially with saturated $NaHCO_3$ (100 ml) and brine (100 ml), dried over $MgSO_4$, filtered and concentrated (at 0°C) to give ~ 2.00 g of the desired isoxazole-4-carbaldehyde (based on estimation from ^{1}H NMR; contaminated with residual EtOH) of suitable purity for use in subsequent reactions. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.01 (s, 1 H), 9.05 (s, 1 H), 8.68 (s, 1 H).

A solution of 4.00 g (11.2 mmol) of amine **54**, 1.03 g (10.6 mmol) of isoxazole-4-carbaldehyde, and 4.750 g (22.4 mmol) of $NaB(OAc)_3H$ in 30 ml of DMF with 1.0 ml of acetic acid was stirred at 25°C for 4 h. The reaction solvents were removed by rotary evaporation. The residue was purified by silica gel column chromatography using 5% MeOH in CH_2Cl_2 as

eluent to give 1.57 g of amine **4038** plus 1.58 g of the imine intermediate. LCMS (ESI) *m/e* 439 $(M+H)^+$.

Method B

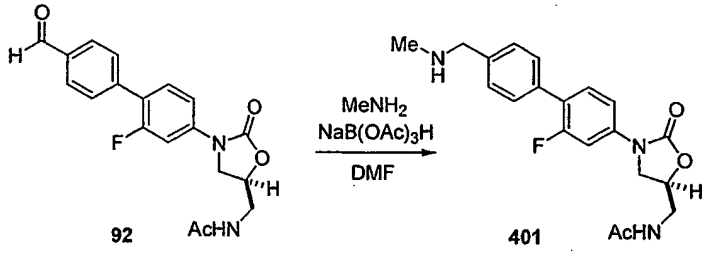
A solution of 1.00 g (5.05 mmol) of isoxazol-4-ylmethyl-carbamic acid tert-butyl ester in 10 ml of 4.0 N HCl in dioxane was stirred at 25°C for 6 h. The reaction mixture was then diluted with 30 ml of diethyl ether and filtered. The solid was washed with diethyl ether and dried to give 0.65 g of *C*-isoxazol-4-yl-methylamine hydrochloride salt of suitable purity for use in subsequent reactions. ^{1}H NMR (300 MHz, DMSO): δ 9.02 (s, 1 H), 8.68 (s, 1 H), 3.94 (q, J = 6, 1 H).

A solution of aldehyde **92** (0.150 g, 0.42 mmol), *C*-isoxazol-4-yl-methylamine hydrochloride salt (0.068 g, 0.51 mmol) obtained above, and $NaB(OAc)_3H$ (0.268 g, 1.26 mmol) in 5 ml of DMF was stirred at 25°C for 2 h. The reaction solvent was removed by rotary evaporation, and the residue was purified by preparative thin-layer chromatography to give 0.160 g of amine **4038**. LCMS (ESI) *m/e* 439 $(M+H)^+$.

Example 53 - Synthesis of Amine 4215

Scheme 34 depicts the synthesis of amine **401** used in the synthesis of compound **4215**.

Scheme 34



Synthesis of amine 401

A solution of aldehyde **92** (3.56 g, 10.0 mmol) in anhydrous DMF (20 mL) was treated with a 2 N solution of methylamine in THF (25 mL, 50.0 mmol) and sodium triacetoxyborohydride (3.20 g, 15.0 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 6 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was quenched with H_2O (40 mL), and the resulting mixture was stirred at room temperature for 30 min. The solid precipitate was then collected by filtration, washed with H_2O (2 x 50 mL), and dried *in vacuo*. This crude material was

subsequently purified by flash column chromatography (5–15 % MeOH-CH_2Cl_2 gradient elution) to afford amine **401** (2.26 g; 61%) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.03 (s, 3H, $COCH_3$), 2.46 (s, 3H, NMe), 3.62 (t, 2H, J = 5.4 Hz), 3.86 (s, 2H, Ar-CH_2)), 3.96 (dd, 1H, J = 6.4, 9.2 Hz), 4.35 (t, 1H, J = 9.2 Hz), 4.90 – 4.99 (m, 1H), 7.58 – 7.80 (m, 7H, aromatic-*H*), 8.45 (t, 1H, J = 5.8 Hz, N*H*$COCH_3$); LCMS (ESI) *m/z* 372 $(M + H)^+$.

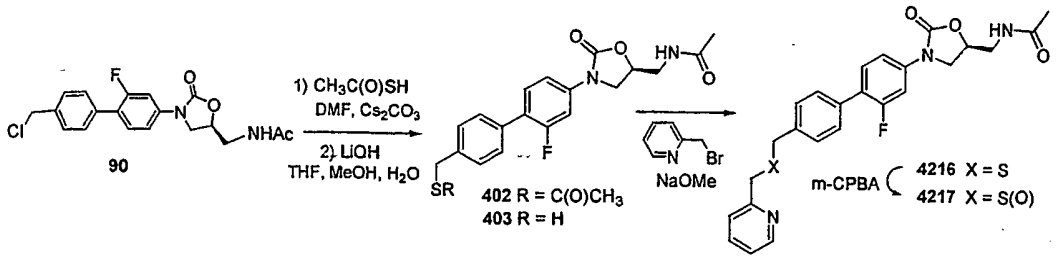
Synthesis of amine 4215

A solution of amine **401** (0.070 g, 0.19 mmol) in methanol (2 mL) and acetic acid (0.020 mL) was treated with quinoline-3-carboxaldehyde (0.033 g, 0.21 mmol) and sodium triacetoxyborohydride (0.080 g, 0.38 mmol) and stirred at 23°C for 2 h. Additional sodium triacetoxyborohydride (0.080 g, 0.38 mmol) and acetic acid (0.020 mL) were added, and the reaction mixture was stirred for 16 h. The solvent was removed *in vacuo*, and the residue was dissolved in THF (3 mL) and acetic acid (0.020 mL) and treated with quinoline-3-carboxaldehyde (0.015 g, 0.095 mmol) and sodium triacetoxyborohydride (0.080 g, 0.38 mmol) and stirred for 9 h. Additional sodium triacetoxyborohydride (0.080 g, 0.38 mmol) was added, and the reaction mixture was stirred for 60 h. The reaction mixture was diluted with methylene chloride (30 mL) and washed with saturated aqueous sodium bicarbonate (25 mL). Drying over Na_2SO_4 and evaporation of solvent yielded crude product, which was purified by flash chromatography (18:1:0.1 methylene chloride:methanol:ammonium hydroxide, 5-10% methanol in 1:1 methylene chloride:ethyl acetate) to afford amine **4215** as a solid (0.030 g, 0.059 mmol; 31%). LCMS (ESI) *m/z* 513 $(M + H)^+$.

Example 54 - Synthesis of Sulfide 4216 and Sulfoxide 4217

Scheme 35 depicts the synthesis of compounds **4216** and **4217**. Benzyl chloride **90** is displaced with thiolacetic acid to afford thioacetate **402**. Hydrolysis of **402** afforded thiol **403** which was alkylated with 2-bromomethyl pyridine to yield sulfide **4216**. Oxidation of **4216** then provided sulfoxide **4217**.

Scheme 35



Synthesis of chloride 90

Alcohol **51** (3.0 g, 8.4 mmol) was dissolved in CH_2Cl_2 (20 mL) and Hunig's base (2 mL). Methanesulfonyl chloride (1.4 mL, 12.6 mmol) was added dropwise and the resulting solution stirred at rt for 4 h. The mixture was poured into 100 mL sat. aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give 3.9 g of an oily yellow solid. The crude material was purified by silica gel chromatography to give chloride **90** as an off-white solid (2.7 g, 7.2 mmol). LCMS (ESI) *m/z* 377 $(M + H)^+$, 418 $(M + CH_3CN + H)^+$, 440 $(M + CH_3CN + Na)^+$.

Synthesis of thioester 402

Under an argon atmosphere, thiolacetic acid (1.55 mL, 21.7 mmol) was added to a mixture of chloride **90** (4.08 g, 10.8 mmol) and Cs_2CO_3 (3.52 g, 10.8 mmol) in DMF (25 mL). The reaction was stirred at room temperature for 2 hours. Then 50 mL of water was added. The off-white product **402** (4.3 g) was collected by filtration in a yield of 96%. LCMS (ESI) *m/z* 417 $(M + H)^+$.

Synthesis of thiol 403

LiOH (360 mg, 15 mmol) was added to a solution of **402** (4.3 g, 10.3 mmol) in a mixture of THF (50 mL), MeOH (50 mL) and water (20 mL). After stirring for 30 minutes at room temperature under argon atmosphere, the insoluble solid was removed by filtration. The filtrate was diluted with water (50 mL), concentrated to remove organic solvents, then neutralized with 10% HCl. The off-white product **403** (3.5 g) was collected by filtration in a yield of 91%. LCMS (ESI) *m/z* 375 $(M + H)^+$.

Synthesis of sulfide 4216

A solution of sulfide **403** (0.20 g, 0.54 mmol) in tetrahydrofuran (1.3 mL), methanol (1.3 mL), and dimethylformamide (1.3 mL) was treated with sodium methoxide (25% in methanol, 0.24 mL, 1.1 mmol) and 2-(bromomethyl)pyridine and stirred at 23°C for 0.5 h. The reaction mixture was diluted with methylene chloride (25 mL), washed with water (25 mL), and the water layer was extracted with methylene chloride (25 mL). The combined organic fractions were dried over Na_2SO_4, and evaporated *in vacuo* to yield crude product, which was purified by preparative thin-layer chromatography (5% methanol/methylene chloride) to afford **4216** as a white powder (0.12 g, 0.26 mmol; 48%). LCMS (ESI) *m/z* 466 $(M + H)^+$.

Synthesis of sulfoxide 4217

A solution of **4216** (0.11 g, 0.23 mmol) in methylene chloride (2.3 mL) was treated with 3-chloroperoxybenzoic acid (0.051 g, 0.23 mmol) and stirred at 23°C for 15 minutes. The solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography (5% methanol/methylene chloride) to afford **4217** as a white powder (0.093 g, 0.19 mmol; 83 %). LCMS (ESI) *m/z* 482 $(M + H)^+$.

Example 55 – Synthesis of Compounds 4218-4220

Synthesis of amine 4218

A solution of amine **54** (0.600 g, 1.68 mmol), 1-methyl-indole-3-carboxaldehyde (0.254 g, 1.60 mmol), and $NaB(OAc)_3H$ (0.712 g, 3.36 mmol) in 30 ml of MeOH with a few drops of acetic acid was stirred at 25°C for 24 h. The reaction solvents were removed by rotary evaporation. The residue was purified by preparative TLC plate to give 0.070 g of amine **4218**. LCMS (ESI) *m/z* 501 $(M + H)^+$.

Synthesis of amine 4219

A solution of amine **54** (0.060 g (0.17 mmol), tetrahydrofuran-3-carboxaldehyde (0.016 g, 0.16 mmol), and $NaB(OAc)_3H$ (0.071 g, 0.34 mmol) in 5 ml of MeOH with a few drops of acetic acid was stirred at 25°C for 6 h. The reaction solvents were removed by rotary evaporation. The residue was purified by preparative TLC plate to give 0.057 g of amine **4219**. LCMS (ESI) *m/z* 442 $(M + H)^+$.

Synthesis of amine 4220

A solution of amine **54** (0.500 g, 1.40 mmol), 1,2,3-thiadiazole-4-carboxaldehyde (0.152 g, 1.33 mmol), and $NaB(OAc)_3H$ (0.594 g, 2.80 mmol) in 8 ml of DMF with a few drops of acetic acid was stirred at 25°C for 2 h. The reaction solvents were removed by rotary evaporation. The residue was purified by preparative TLC to give 0.484 g of amine **4220**. LCMS (ESI) *m/z* 492 $(M + H)^+$.

Example 56 – Synthesis of Compound 4221

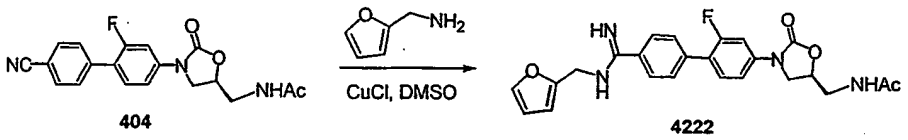
A solution of amine **54** (79.0 mg, 0.22 mmol) in anhydrous DMF (3 mL) was treated with 3-(2-oxo-1,2-dihydro-pyridin-3-yl)-acrylic acid (36.3 mg, 0.22 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (62.7 mg, 0.33 mmol) at room temperature, and the resulting reaction mixture was stirred at 25°C for 12 h. When TLC and

LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0–7% MeOH-CH_2Cl_2 gradient elution) to afford amide **4221** (45.5 mg; 41%) as a white solid. LCMS (ESI) *m/z* 505 $(M + H)^+$.

Example 57 – Synthesis of Amidine 4222

Scheme 36 illustrates the synthesis of amidine **4222**. Nitrile **404** and furfurylamine were heated together in the presence of copper chloride to yield amidine **4222**.

Scheme 36



Synthesis of nitrile 404

This compound was made from 4-cyanophenylboronic acid and iodide **50** as described above for the synthesis of alcohol **51**.

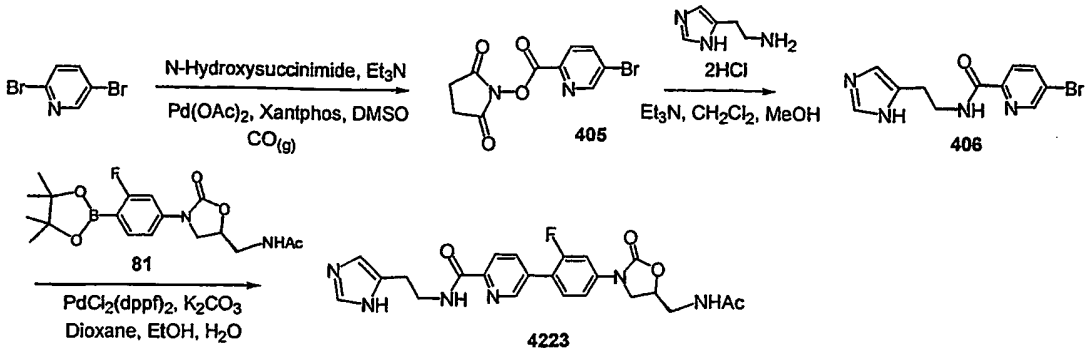
Synthesis of amidine 4222

Under an argon atmosphere, a mixture of nitrile **404** (98 mg, 0.28 mmol), furfurylamine (27 mg, 0.28 mmol) and copper (I) chloride (CuCl, 28 mg, 0.28 mmol) in DMSO (2 mL) was heated at 80°C for 48 h. The reaction was diluted with CH_2Cl_2, washed with saturated Na_2CO_3 and dried under vaccum. The crude product was purified by chromatography (5:1:0.05 CH_2Cl_2/ MeOH/$NH_3.H_2O$) to afford **4222** (14 mg; 11%). LCMS (ESI) *m/z* 451 $(M + H)^+$.

Example 58 – Synthesis of Amide 4223

Scheme 37 illustrates the synthesis of amide **4223**. 2,5-Dibromopyridine is converted to activated pyridyl ester **405** which is then treated with histamine to provide amide **406**. The Suzuki coupling of **406** and boronate **81** gave the final target amide **4223**.

Scheme 37



Synthesis of ester 405

Under an argon atmosphere, triethylamine (0.31 mL, 2.25 mmol) was added to a mixture of 2,5-dibromopyridine (355 mg, 1.5 mmol), palladium acetate (16.8 mg. 0.075 mmol), Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, 43.4 mg, 0.075 mmol) and *N*-hydroxysuccinimide (241.5 mg, 2.1 mmol) in DMSO (2 mL). The solution was purged with carbon monoxide for 15 min and stirred under a carbon monoxide balloon at 80°C for 16 h. The reaction mixture was then cooled to room temperature, diluted with 20 mL of ethyl acetate and washed with saturated sodium bicarbonate solution and water. The organic phase was dried over sodium sulfate and evaporated to give crude product. Chromatography on silica gel using hexane:acetone (3:1) provided ester **405** (75 mg; 17%). ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.85 (m, 1H), 8.06 (m, 2H), 2.90 (s, 4H) .

Synthesis of amide 406

A mixture of active ester **405** (350 mg, 1.17 mmol), histamine dihydrochloride (216 mg, 1.17 mmol) and Et_3N (0.33 mL, 2.34 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 1 h. The reaction was washed with brine and dried under vaccum. The crude product was purified by chromatography (15:1:0.05 CH_2Cl_2/MeOH/$NH_3.H_2O$) to afford **406** (280 mg; 81%). LCMS (ESI) *m/z* 295 $(M + H)^+$.

Synthesis of amide 4223

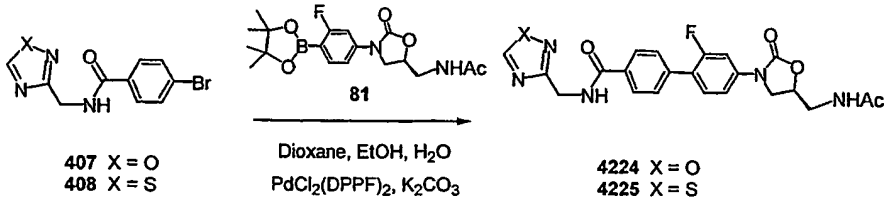
Under an argon atmosphere, a mixture of **406** (230 mg, 0.78 mmol), boronate **81** (295 mg, 0.78 mmol), $Pd(dppf)_2Cl_2$ (19 mg, 0.023 mmol) and K_2CO_3 (323 mg, 2.34 mmol) in 5 mL of a mixture of dioxane/EtOH/H_2O (3:1:1) was heated at 100°C for 12 h. The reaction was concentrated and the residue was dissolved in MeOH (2 mL) and CH_2Cl_2 (10 mL). Inorganic salts were removed by filtration. The filtrate was concentrated and purified by chromatography

(15:1:0.05 CH_2Cl_2/MeOH/$NH_3.H_2O$) to afford amide **4223** (106 mg; 29%). LCMS (ESI) *m/z* 467 $(M + H)^+$.

Example 59 – Synthesis of Amides 4224 and 4225

Scheme 38 illustrates the synthesis of amides **4224** and **4225**. Aryl bromides **407** and **408** were coupled to boronate **81** to afford **4224** and **4225** respectively.

Scheme 38



Synthesis of amide 4224

A mixture of 4-bromobenzoyl chloride (110 mg, 0.5 mmol), 1,2,4-oxadiazol-3-yl-methylamine hydrochloride (68 mg, 0.5 mmol), DMF (1 drop) and Et_3N (0.33 mL, 2.34 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 4 h. The reaction was washed with brine and dried under vaccum to afford crude amide **407**. The amide **407** obtained was added to a mixture of boronate **81** (189 mg, 0.5 mmol), $Pd(dppf)_2Cl_2$ (20 mg, 0.025 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in 5 mL of dioxane/EtOH/H_2O (3:1:1) under an argon atmosphere. After being heated at 100°C for 12 h, the reaction was diluted with water and MeOH, and then filtered through celite. The filtrate was concentrated to remove organic solvent. The crude product was collected by filtration and further purified by chromatography (25:1:0.05 CH_2Cl_2/MeOH/$NH_3.H_2O$) to afford **4224** (45 mg; 32%). LCMS (ESI) *m/z* 452 $(M - H)^+$.

Synthesis of amide 4225

A mixture of 4-bromobenzoyl chloride (29 mg, 0.132 mmol), 1,2,4-thiadiazol-3-yl-methylamine hydrochloride (20 mg, 0.132 mmol), DMF (1 drop) and Et_3N (27 mg, 0.264 mmol) in THF (4 mL) was stirred at room temperature for 2 h. The reaction was concentrated, dissolved in CH_2Cl_2, washed with brine and dried under vaccum to afford crude amide **408**. The resultant amide **408** obtained above was added to a mixture of boronate **81** (50 mg, 0.132 mmol), $Pd(dppf)_2Cl_2$ (6 mg, 0.0066 mmol) and K_2CO_3 (55 mg, 0.396 mmol) in 2 mL of dioxane/EtOH/ H_2O (3:1:1) under an argon atmosphere. After being heated at 100°C for 12 h, the reaction was concentrated, dissolved in EtOAc, washed with brine and dried under vaccum. The crude product was purified by chromatography on silica gel (25:1:0.05

CH_2Cl_2/MeOH/$NH_3.H_2O$) to afford amide **4225** (30 mg; 48%). LCMS (ESI) *m/z* 470 $(M + H)^+$.

Example 60 – Synthesis of Sulfide 4226

Under an argon atmosphere, sodium methoxide (NaOMe, 25% by wt. in MeOH, 95 mg, 0.44 mmol) was added to a solution of thiol **403** (75 mg, 0.2 mmol) and epibromohydrin (30 mg, 0.22 mmol) in MeOH (3 mL) and THF (3 mL). After stirring at room temperature for 2 h, the reaction was concentrated. The residue was dissolved CH_2Cl_2, washed with brine, dried over $MgSO_4$ and concentrated under vaccum. The crude product was purified by chromatography on silica gel (25:1:0.05 CH_2Cl_2/MeOH/$NH_3.H_2O$) to afford sulfide **4226** (55 mg; 61% as a mix of diastereomers). LCMS (ESI) *m/z* 453 $(M + Na)^+$.

Example 61 – Synthesis of Amines 4227-4229

Synthesis of amine 4227

A suspension of aldehyde **92** (107 mg, 0.3 mmol) in anhydrous THF (2 mL) and anhydrous methanol (MeOH, 2 mL) was treated with 2-(1*H*-imidazol-4-yl)-ethylamine (110.0 mg, 0.6) and sodium triacetoxyborohydride (127 mg, 0.6 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 6 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. This residue was directly purified by flash column chromatography (0–10% MeOH-CH_2Cl_2 gradient elution) to afford amine **4227** (24 mg, 135.3 mg; 18%) as an off-white solid. LCMS (ESI) *m/z* 452 $(M + H)^+$.

Synthesis of amine 4228

A suspension of aldehyde **92** (107 mg, 0.3 mmol) in anhydrous THF (2 mL) and anhydrous methanol (MeOH, 2 mL) was treated with 2-(5-methyl-1*H*-indol-3-yl)-ethylamine hydrochloride (126.0 mg, 0.6 mmol) and sodium triacetoxyborohydride (127 mg, 0.6 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 12 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. This residue was directly purified by flash column chromatography (0–10% MeOH-CH_2Cl_2 gradient elution) to afford amine **4228** (32 mg; 21%) as off-white solids. LCMS (ESI) *m/z* 515 $(M + H)^+$.

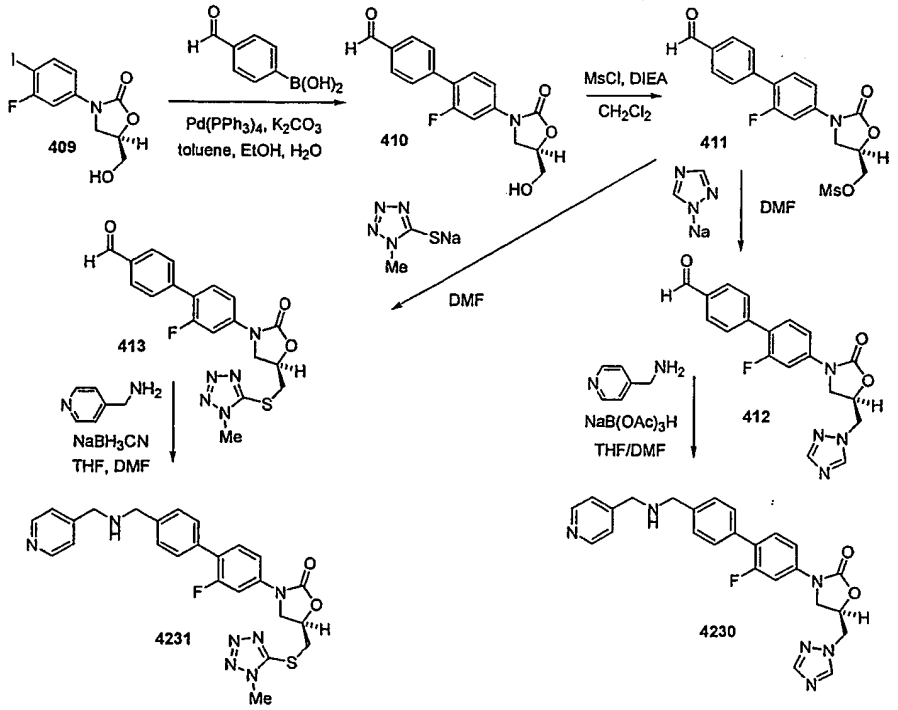
Synthesis of amine 4229

A suspension of aldehyde **92** (107 mg, 0.3 mmol) in anhydrous THF (2 mL) and anhydrous methanol (2 mL) was treated with (5-methyl-isoxazol-3-yl)-methylamine (67.0 mg, 0.6 mmol) and sodium triacetoxyborohydride (127 mg, 0.6 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 12 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. This residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford amine **4229** (34 mg; 25%) as an off-white solid. LCMS (ESI) *m/z* 453 $(M + H)^+$.

Example 62 – Synthesis of Amines 4230 and 4231

Scheme 39 shows the synthesis of amines **4230** and **4231**. Known alcohol **409** (*see* U.S. Patent Nos. 5,523,403 and 5,565,571) is coupled to 4-formylphenylboronic acid to afford alcohol **410** which is then converted to mesylate **411**. Alkylation of mesylate **411** with the appropriate nucleophiles affords biaryl aldehydes **412** and **413** which are transformed to amines **4230** and **4231** respectively by reductive amination chemistry.

Scheme 39



Synthesis of alcohol 410

A suspension of alcohol **409** (5.07 g, 15.0 mmol) in toluene (30 mL) was treated with 4-formylphenylboronic acid (3.15 g, 21.0 mmol), K_2CO_3 (6.22 g, 45.0 mmol), EtOH (10 mL), and H_2O (10 mL) at 25°C, and the resulting mixture was degassed three times under a steady stream of argon at 25°C. $Pd(dppf)_2Cl_2$ (370 mg, 0.45 mmol) was subsequently added to the reaction mixture, and the resulting reaction mixture was degassed three times again before being warmed to gentle reflux for 2 h. When TLC and LCMS showed the coupling reaction was complete, the reaction mixture was cooled to room temperature before being treated with H_2O (100 mL). The resulting mixture was then stirred at room temperature for 10 min before being cooled to 0–5°C for 1 h. The solid precipitate was collected by filtration, washed with H_2O (2 x 40 mL) and 20% EtOAc/hexane (2 X 40 mL), and dried *in vacuo*. The crude alcohol **410** (4.62 g; 98%) was obtained as a brown solid, which by HPLC and ^1H NMR was found to be of suitable purity to be used in subsequent reactions. LCMS (ESI) *m/z* 316 $(M + H)^+$.

Synthesis of mesylate 411

A solution of the crude alcohol **410** (4.2 g, 13.3 mmol) in CH_2Cl_2 (50 mL) was treated with diisopropylethylamine (2.6 g, 3.5 mL, 20.0 mmol) at 25°C, and the resulting mixture was cooled to 0–5°C before being treated dropwise with methanesulfonyl chloride (1.83 g, 1.25 mL, 16.0 mmol) at 0–5°C. The resulting reaction mixture was subsequently stirred at 0–5°C for 2 h. When TLC and LCMS showed the reaction was complete, the reaction mixture was treated with H_2O (50 mL) at 0-5°C. The mixture was then concentrated *in vacuo* to remove most of the CH_2Cl_2, and the resulting slurry was treated with H_2O (50 mL). The mixture was stirred at room temperature for 10 min before being cooled to 0–5°C for 30 min. The solid precipitate was collected by filtration, washed with H_2O (2 x 40 mL) and 20% EtOAc/hexane (2 x 20 mL), and dried *in vacuo*. The crude mesylate **411** (4.60 g; 88%) was obtained as a brown solid, which by ^1H NMR and HPLC was found to be of suitable purity to be used in subsequent reactions. LCMS (ESI) *m/z* 394 $(M + H)^+$.

Synthesis of aldehyde 412

A solution of mesylate **411** (393 mg, 0.1 mmol) in anhydrous DMF (4 mL) was treated with 1*H*-1,2,4-triazole sodium salt (100 mg, 1.1 mmol) at room temperature, and the resulting reaction mixture was warmed to 40°C and stirred at 40°C for 4 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. This

residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford aldehyde **412** (318.4 mg; 87%) as an off-white solid. LCMS (ESI) *m/z* 367 $(M + H)^+$.

Synthesis of amine 4230

A suspension of aldehyde **412** (90.0 mg, 0.25 mmol) in anhydrous THF (2 mL) and anhydrous DMF (2 mL) was treated with C-pyridin-4-yl-methylamine (29.0 mg, 0.27 mmol) and sodium triacetoxyborohydride (106.0 mg, 0.5 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 6 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. This residue was directly purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford amine **4230** (47.0 mg; 41%) as an off-white solid. LCMS (ESI) *m/z* 459 $(M + H)^+$.

Synthesis of aldehyde 413

A solution of 1-methyl-1*H*-tetrazole-5-thiol sodium salt (174.0 mg, 1.5 mmol) in anhydrous THF (5 mL) was treated with NaH (60% oil dispersion in mineral oil, 60.0 mg, 1.5 mmol) at 0–5°C, and the resulting reaction mixture was stirred at 0–5°C for 1 h. The mixture was then treated with mesylate **411** (393.0 mg, 1.0 mmol) and anhydrous DMF (5 mL) at 0–5°C, and the resulting reaction mixture was gradually warmed to room temperature before being warmed to 40°C for 4 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. This residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford aldehyde **413** (272.6 mg; 66%) as an off-white solid. LCMS (ESI) *m/z* 414 $(M + H)^+$.

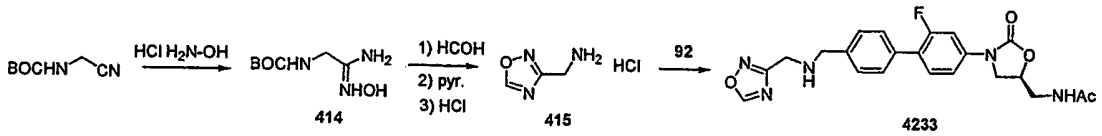
Synthesis of amine 4231

A suspension of aldehyde **413** (100.0 mg, 0.24 mmol) in anhydrous THF (2 mL) and anhydrous DMF (2 mL) was treated with C-pyridin-4-yl-methylamine (29.0 mg, 0.27 mmol) and sodiumborohydride (15.0 mg, 0.24 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 12 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. This residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford amine **4231** (44.0 mg; 36%) as an off-white solid. LCMS (ESI) *m/z* 506 $(M + H)^+$.

Example 63 – Synthesis of Amine 4233

Scheme 40 shows the synthesis of isoxadiazole **4233**. BOC-Aminoacetonitrile was converted to hydroxyamidine **414** which was then cyclyzed to isoxadiazole **415**. Reductive amination of **415** with aldehyde **92** afforded amine **4233**.

Scheme 40



Synthesis of hydroxyamidine 414

To a solution of BOC-aminoacetonitrile (6.0 g, 38 mmol) in EtOH (60 mL) was added 50% aq. hydroxylamine (4.5 mL, 77 mmol) and the mixture was refluxed for 5 h. The solvents were evaporated and the residue redissolved in CH_2Cl_2 (100 mL), dried over Na_2SO_4 and again evaporated, yielding hydroxyamidine **414** (7 g; 96%). ^{1}H-NMR, (300 MHz, $CDCl_3$) δ 5.43-5.39 (m 1H), 5.12-5.03 (m, 3H), 3.75 (d, J = 5 Hz, 2H), 1.46 (s, 9H).

Synthesis of isoxadiazole 415

To a solution of **414** (2.8 g, 14.7 mmol) in CH_2Cl_2 (45 mL) was added Et_3N (4.1 mL, 29.5 mmol), formic acid (0.72 mL, 19.2 mmol), EDCI (4.24 g, 22 mmol), and DMAP (89 mg, 0.7 mmol). The mixture was stirred at room temperature for 3 h, evaporated to ca. 15 mL, diluted with ethyl acetate (50 mL), washed with 1M citric acid (20 mL), water (2 x 20 mL), brine (1 x 20 mL), dried over Na_2SO_4 and the solvent evaporated. The crude residue was dissolved in pyridine (11 mL) and stirred at 105°C for 4.5 h, poured into 1M citric acid-ice (100 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with water (2 x 15 mL), brine (1 x 15 mL), dried over Na_2SO_4 and the solvent evaporated. The residue was dissolved in 4M HCl in dioxane (7 mL). The mixture was stirred at room temperature for 2 h and then evaporated and diluted with ether (3 mL). The solution was filtered and the solid was washed with ether (2 x 5 mL) and dried under high vacuum to yield **415** (855 mg; 83%). ^{1}H-NMR, (300 MHz, d_6-DMSO) δ 9.6 (s, 1H), 8.77 (br s, 3H), 4.09 (m, 2H).

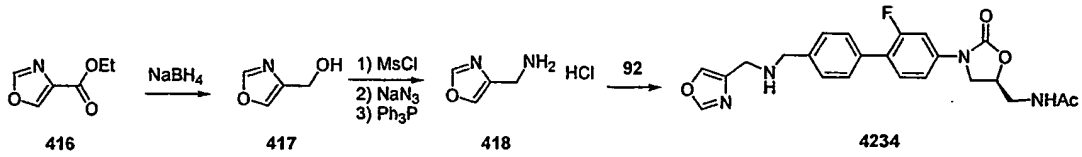
Synthesis of amine 4233

Amine **4233** was synthesized from **415** and aldehyde **92** using the same conditions described in Example 53 for the synthesis of amine **401** from aldehyde **92**. LCMS (ESI) *m/z* 441 $(M + H)^+$.

Example 64 – Synthesis of Amine 4234

Scheme 41 depicts the synthesis of amine **4234**. Known ester **416** (*Liebigs Annalen der Chemie* **1979**, 1370) was reduced to alcohol **417** which was manipulated to amine salt **418** via standard chemistry. Reductive amination of **418** with aldehyde **19** yielded amine **4234**.

Scheme 41



Synthesis of alcohol 417

To a solution of the oxazole **416** (500 mg, 4.4 mmol) in MeOH (20 mL) was added sodium borohydride ($NaBH_4$, 540 mg, 17.5 mmol). The mixture was stirred at room temperature for 2 h, then $NaBH_4$ (540 mg, 17.5 mmol) was added. After 1 h an additional amount of $NaBH_4$ (270 mg, 9.0 mmol) was added. After stirring for 2 h, the mixture was quenched with 5% Na_2CO_3 (2 mL) and evaporated. The crude residue was purified on silica gel eluting with ether, yielding **417** as a clear oil (300 mg; 86%). ^{1}H-NMR, (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.57 (s, 1H), 4.57 (s, 2 H).

Synthesis of amine hydrochloride 418

Alcohol **417** was converted to amine salt **418** following the procedure described above to make amine **54** from alcohol **51**. The crude material was taken up HCl in dioxane and then triturated with ether to isolate the salt as was described above for amine salt **415**.

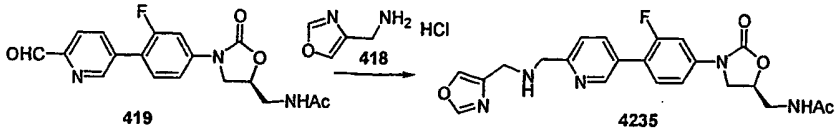
Synthesis of amine 4234

This amine was synthesized from **418** and aldehyde **92** using the same conditions described above for the synthesis of amine **401** from aldehyde **92**. LCMS (ESI) *m/z* 439 $(M + H)^+$.

Example 65 – Synthesis of Amine 4235

Scheme 42 depicts the synthesis of amine **4235** from aldehyde **419** and amine salt **418**.

Scheme 42



Synthesis of aldehyde 419

Aldehyde **419** was synthesized from 5-bromo-pyridine-2-carboxaldehyde and boronate ester **81** as described above for the synthesis of amide **4223**.

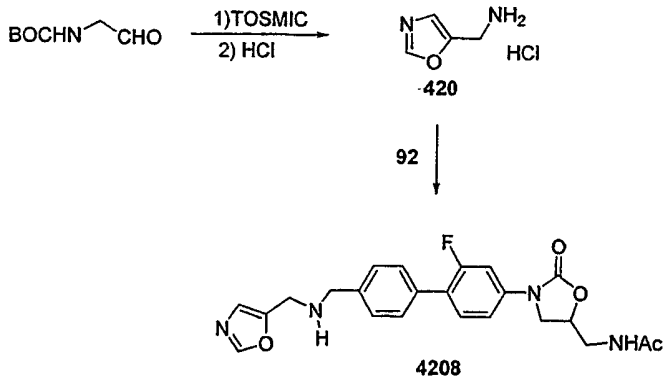
Synthesis of amine 4235

Amine **4235** was synthesized from aldehyde **419** and amine salt **418** using the same conditions described in Example 53 for the synthesis of amine **401** from aldehyde **92**. LCMS (ESI) *m/z* 440 $(M + H)^+$.

Example 66 – Synthesis of Compound 4208

Scheme 43 depicts the synthesis of compound **4208**.

Scheme 43



To a solution of *tert*-Butyl *N*-(2-oxoethyl)carbamate (4.0g, 25.1 mmol) in MeOH (80 mL) was added K_2CO_3 (10.4 g, 75.4 mmol) followed by tosylmethylisocyanide (TOSMIC, 4.91 g, 25.1 mmol). The suspension was refluxed for 1h and then evaporated. The residue was poured into ice-water (100 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water (2x 20 mL), brine (1x 20 mL), dried over Na_2SO_4 and evaporated. The residue was purified on silica gel eluting with hexanes/ethyl acetate 1:1,

yielding a faint yellow oil which was directly dissolved in 4 M HCl in dioxane (15 mL), stirred for 45 min., and evaporated. The residue was crystallized with ether (10mL) and filtered, yielding amine **420** (1.50g, 42%). ^{1}H-NMR, (300 MHz, d-DMSO δ 8.73 (br.s 3H), 8.48 (s, 1H), 7.28 (s, 1H), 4.20-4.12 (m, 2H).

Compound **4208** was synthezised from amine **420** and aldehyde **92** using the same conditions described in Example 53 for the synthesis of amine **401** from aldehyde **92**. LCMS (ESI): 439.1 $(M + H)^+$.

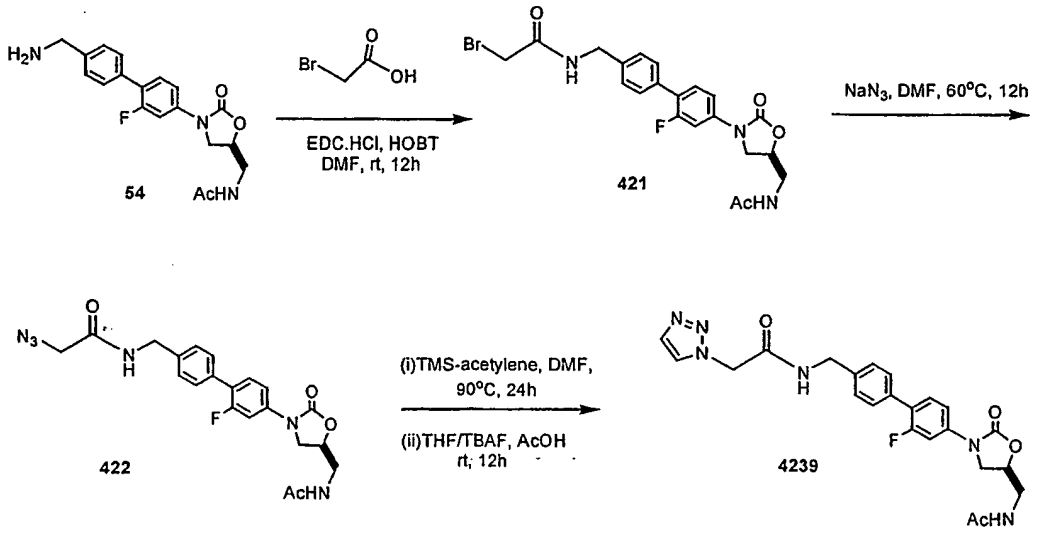
Example 67 – Synthesis of Compound 4136

A solution of amine **54** (0.070 g, 0.20 mmol) in DMF (1.0 ml) was treated with triethylamine (0.055 ml, 0.40 mmol) and 2-phthalimidoethanesulfonyl chloride (0.059 mg, 0.22 mmol) and stirred at 23 °C for 3.5 h. Additional 2-phthalimidoethanesulfonyl chloride (0.081 mg, 0.30 mmol) and triethylamine (0.087 ml, 0.63 mmol) were added, and the reaction mixture was stirred for 16 h. The reaction mixture was diluted with methylene chloride (20 ml), washed with 1 M hydrochloric acid (20 ml), and washed with saturated aqueous sodium bicarbonate (20 ml). Drying over Na_2SO_4 and evaporation of solvent yielded crude product, which was purified by flash chromatography (2.5-5% methanol in 1:1 methylene chloride/ethyl acetate) to afford compound **4136** (0.082 g, 0.14 mmol, 70%). MS (ESI): 617 $(M+Na)^+$.

Example 68 – Synthesis of Compound 4239

Scheme 44 depicts the synthesis of compound **4208**.

Scheme 44



Synthesis of azide 422

To a solution of bromoacetic acid (1.0g, 2.8 mmol) and 1-hydroxybenzotriazole hydrate (HOBT, 0.44g, 3.4 mmol) in DMF (15 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl, 0.66g, 3.4 mmol) and amine **54** (0.45g, 3.2 mmol) in a rapid succession. The resulting mixture was stirred at room temperature overnight. The solvent was evaporated and the crude product was suspended in water (about 40 mL). The suspension was filtered and the residue was washed with water, diethyl ether (about 50 mL) and dried *in vacuo* to give analytically pure compound **421** as white solid in quantitative yield.

Compound **421** was dissolved in DMF (10 mL) and NaN_3 (0.55g, 8.0 mmol) was added. The mixture was heated at 60 °C overnight and solvent evaporated off. The crude was suspended in water (about 40 mL), filtered, and the residue was washed with water, diethyl ether (about 50 mL) and dried *in vacuo* to give analytically pure azide **422** as white solid (0.97g, 69.3%). LCMS (ESI): 441 $(M + H)^+$.

Synthesis of triazole 4239

Azide **422** (0.25g, 0.57 mmol) and TMS-acetylene (0.28g, 2.84 mmol) were dissolved in DMF (5 mL) and the mixture was heated at 90°C for 24h under an argon atmosphere. The solvent was evaporated off, leaving a solid residue. The residue was suspended in water, filtered and dried *in vacuo*. To the solution of this residue in THF (5 mL) was added 1M TBAF in THF (1.14 mL) and acetic acid (0.04 mL, 0.57 mmol), and the mixture was stirred at room temperature overnight, after which time TLC showed a complete consumption of the starting material. The solvent was evaporated off and the crude was suspended in diethyl ether (about 40 mL). The suspension was filtered, and the residue was washed in succession with CH_2Cl_2 (about 50 mL), 10 % CH_3CN in diethyl ether (about 50 mL), diethyl ether (about 20 mL). The residue was air dried to give analytically pure triazole **4239** as white solid (0.238g, 89.6 %). LCMS (ESI): 467.1 $(M + H)^+$.

Example 69 – Synthesis of Compound 4252

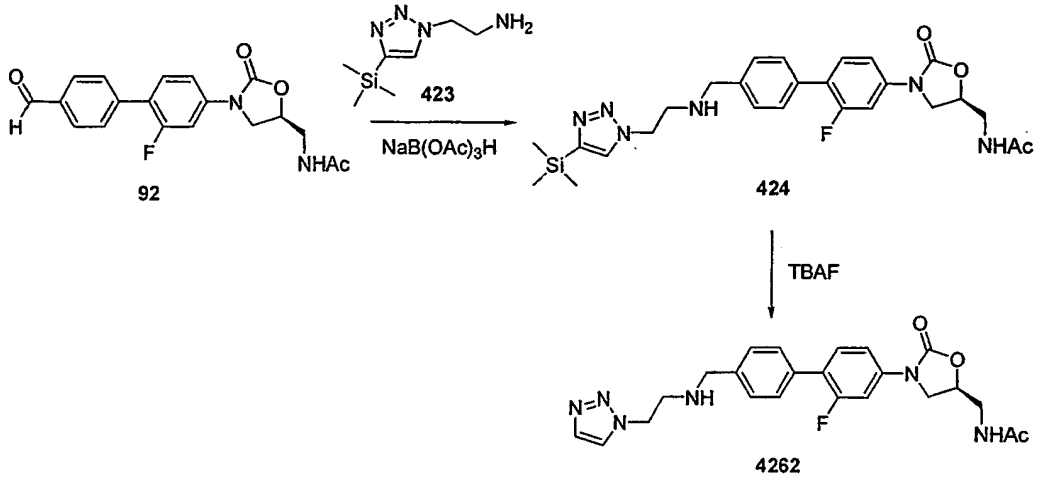
A solution of the methanesulfonic acid 5-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-pyridin-2-ylmethyl ester **106** (220 mg, 0.5 mmol) in DMF (4.0 mL) was treated with C-isoxazol-4-yl-methylamine (68 mg, 0.5 mmol, 1.0 equiv) at room temperature, and the resulting reaction mixture was warmed to 60 °C and stirred for 6 hours. When TLC and MS showed the reaction to be complete, the reaction mixture was concentrated *in vacuo*,

and the residue was directly purified by column chromatography (0–5% MeOH/CH_2Cl_2 gradient elution) to afford the desired N-{3-[3-Fluoro-4-(6-{[(isoxazol-4-ylmethyl)-amino]-methyl}-pyridin-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide **4252** (22 mg, 10%) as off-white solids. LCMS (EI): 440 (M^+ + H).

Example 70 – Synthesis of Compound 4262

Scheme 45 depicts the synthesis of compound **4262**.

Scheme 45



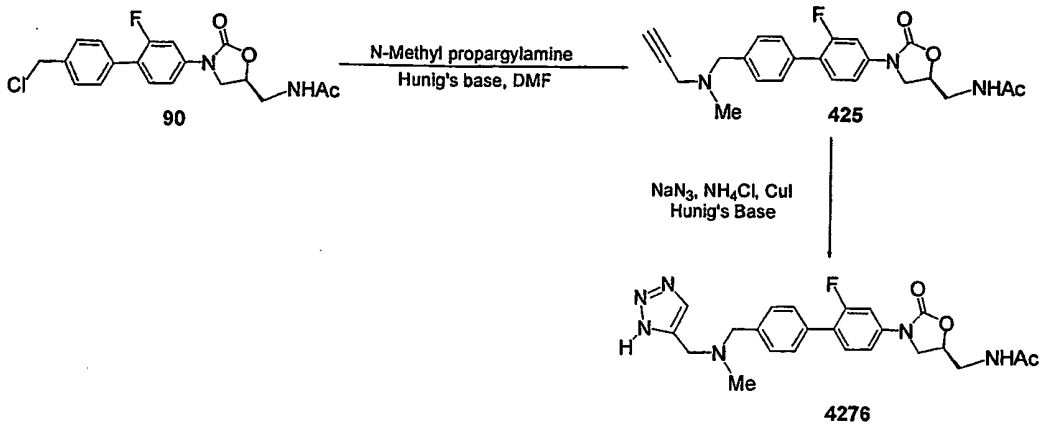
To a solution of 0.060 g (0.17 mmol) of aldehyde **92** and 0.056 g (0.25 mmol) of the HCl salt of amine **423** in 3 ml of DMF was added 0.071 g (0.34 mmol) of $NaB(OAc)_3H$. The reaction mixture was stirred at 25 °C for 2 h. The DMF was removed, and the residue was purified by preparative TLC to give 0.041 g of compound **424**. MS (M+1): 525.

To a solution of 0.012 g (0.023 mmol) of **424** and 0.03ml (0.027 mmol) of TBAF (1 M in THF) in 4 ml of CH_2Cl_2 was added a few drops of acetic acid, and the mixture was stirred at 0 °C for 4 h. The reaction solvents were removed by rotary evaporation, and the residue was purified by preparative TLC to give 0.008 g of compound **4262**. MS (M+1): 489.

Example 71 - Synthesis of Triazole 4276

Scheme 46 depicts the synthesis of triazole **4276**.

Scheme 46



Synthesis of Alkyne 425

To a solution of chloride **90** (2 g, 5.3 mmol) and Hunig's base (diisopropylethylamine, 1.7 mL, 10 mmol) in DMF (15 mL) was added a solution of N-methyl propargylamine (0.55g mg, 8.0 mmol) in DMF (1 mL). After stirring at room temperature for 16 h, the DMF was removed *in vacuo*. The crude product was purified by preparative thin layer chromatography (10:1:0.05 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 2.05 g of alkyne **425** in a yield of 95%. MS (ESI): 410.1 (100%) $(M+Na)^+$.

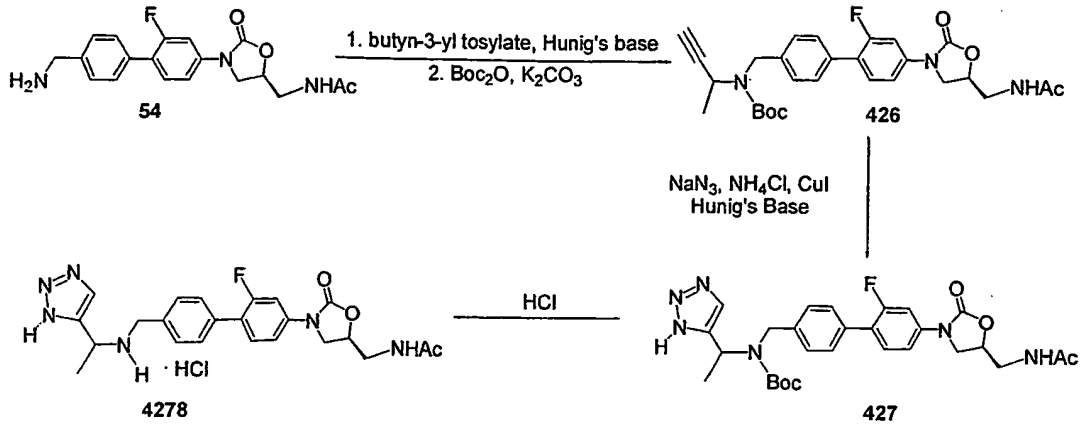
Synthesis of compound 4276

A mixture of alkyne **425** (1.8 g, 4.4 mmol), sodium azide (0.43 g, 6.6 mmol), ammonium chloride (0.35 g, 6.6 mmol), copper(I) iodide (84 mg, 0.44 mmol) and Hunig's base (3.5 mL, 20 mmol) in DMF (10 mL) was heated under argon atmosphere at 80 °C for 48 h. The DMF was removed *in vacuo*, and the residue was dissolved in MeOH (5 mL), CH_2Cl_2 (50 mL), conc. ammonium hydroxide (20 mL) and saturated ammonium chloride solution (20 mL). After stirring at room temperature for 2 h, the organic phase was separated, washed with saturated NH_4Cl solution and water, dried over $MgSO_4$, and concentrated. The crude product was purified by preparative thin layer chromatography (10:1:0.05 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 1.75 mg of triazole **4276** in a yield of 88%. MS (ESI): 453.1 (100%) $(M+H)^+$, 475.2 $(M+Na)^+$.

Example 72 - Synthesis of Triazole 4278

Scheme 47 depicts the synthesis of triazole **4278**.

Scheme 47



Synthesis of alkyne 426

A mixture of amine **54** (422 mg, 1.18 mmol), butyn-3-yl tosylate (265 mg, 1.18 mmol), Hunig's base (diisopropylethylamine, 0.2 mL, 1.15 mmol) and potassium iodide (17 mg, 0.1 mmol) in DMF (5 mL) was heated at 70 °C 15 h. The DMF was removed *in vacuo*. The residue was dissolved in a mixed solvent of THF (10 mL) and water (2 mL), K_2CO_3 (276 mg, 2 mmol), and then di-tert-butyl dicarbonate (218 mg, 1 mmol) was added. The reaction was stirred at room temperature for 12 h, and the THF was removed *in vacuo*. 40 mL of EtOAc was added and the solution was washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by preparative thin layer chromatography (15:1:0.05 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 210 mg of alkyne **426** in a yield of 22%. MS (ESI): 410.1, 532.1 $(M+Na)^+$, 573.1 (100%).

Synthesis of triazole 427

A mixture of alkyne **426** (150 mg, 0.29 mmol), sodium azide (29 mg, 0.44 mmol), ammonium chloride (24 mg, 0.44 mmol), copper(I) iodide (56 mg, 0.29 mmol) and Hunig's base (0.26 mL, 1.5 mmol) in DMF (3 mL) was heated under argon atmosphere at 80 °C for 24 h. The DMF was removed *in vacuo*, and the residue was dissolved in CH_2Cl_2 and conc. ammonium hydroxide solution. The organic phase was separated, washed with saturated NH_4Cl solution and water, dried over $MgSO_4$, and concentrated. The crude product was purified by preparative thin layer chromatography (15:1:0.05 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 155 mg of triazole **427** in a yield of 95%. MS (ESI): 453.1 (100%), 575.1 $(M+Na)^+$.

Synthesis of compound 4278

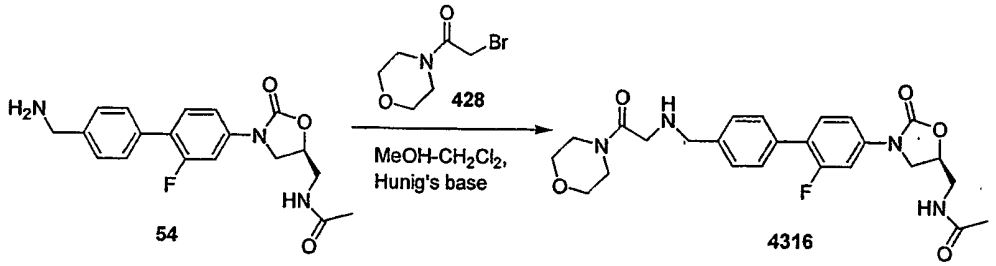
To a solution of triazole **427** (155 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) and MeOH (1 mL) was added 2 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 15 h, the reaction was concentrated and washed with EtOAc/MeOH to give 130 mg of compound **4278** in a yield of 95%. MS (ESI): 453.1.1(100%) $(M+H)^+$.

Example 73 – Synthesis of Compounds 4316 and 4314

Synthesis of morpholine 4316

Scheme 48 depicts the synthesis of morpholine **4316**.

Scheme 48

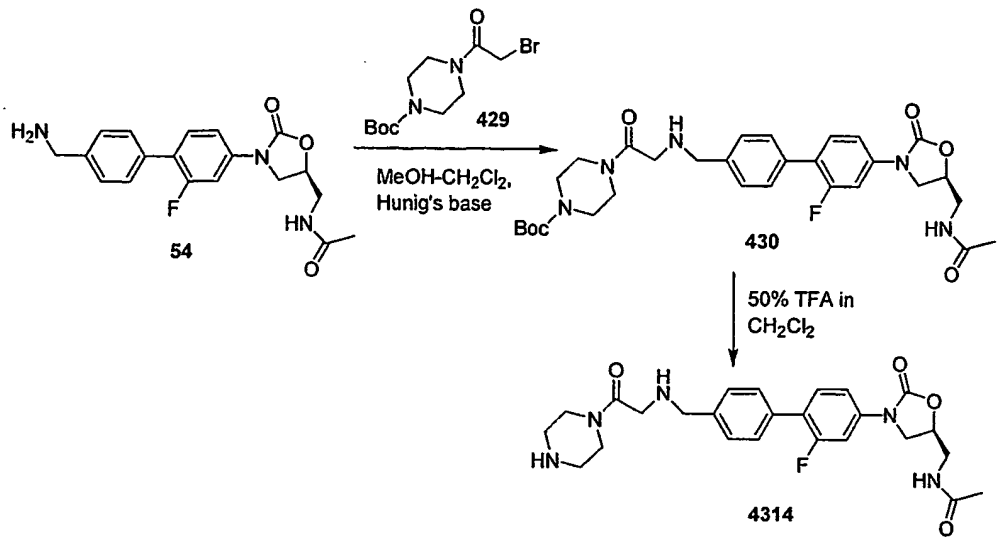


Known bromide **428** was synthesized from morpholine and bromoacetyl bromide as reported in the literature (Thompson, W. J. *et al. J. Med. Chem.* **1992**, *35*, 1685). To a solution of amine **54** (86 mg, 0.23 mmol) in a mixture of methyl alcohol (2 mL), methylene chloride (2 mL) and Hunig's base (2 mL) was added bromide **428** (32 mg, 0.23 mmol) at 0°C. The reaction mixture was warmed to room temperature and heated over an oil bath at 80°C for 18h. The solution was concentrated and purified by flash chromatography over silica gel (14:1:0.05 CH_2Cl_2/MeOH: NH_4OH) to yield 66 mg of compound **4316**. ^{1}HNMR (300 MHz, CD_3OD): δ 7.50-7.22 (m, 7H), 4.77-4.69 (m, 1H), 4.06 (t, J = 9 Hz, 1H), 3.77 (dd, J = 6, 3 Hz, 1H), 3.70 (s, 1H), 3.55-3.46 (m, 8H), 3.39-3.36 (m, 3H), 3.34-3.30 (m, 2H), 1.86 (s, 3H). LCMS (ESI) *m/e* 485 $(M+H)^+$.

Synthesis of piperazine 4314

Scheme 49 depicts the synthesis of piperazine **4314**.

Scheme 49

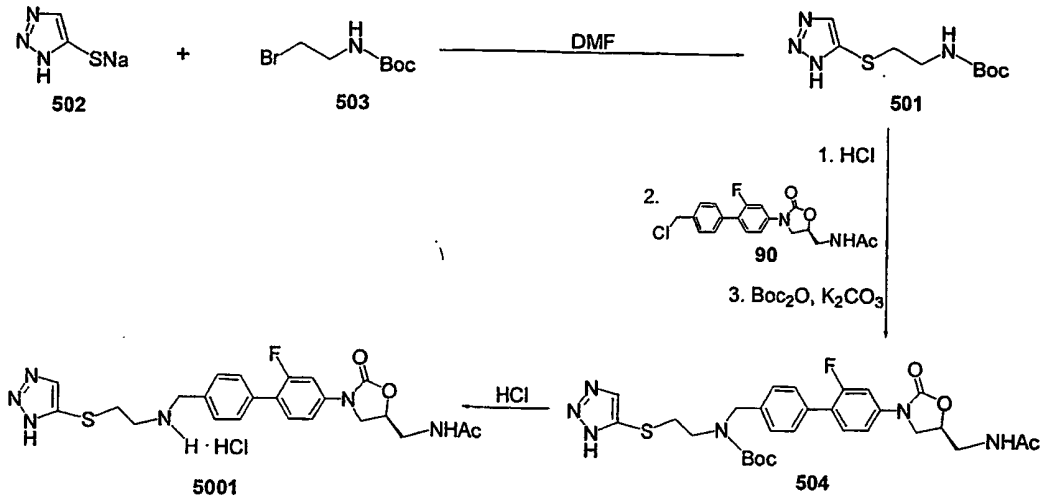


Bromide **429** was synthesized from tert-Butyl 1-piperazine carboxylate and bromoacetyl bromide following literature procedures (Thompson, W. J. *et al. J. Med. Chem.* **1992**, *35*, 1685). ^{1}HNMR (300 MHz, $CDCl_3$): δ 3.86 (s, 2H), 3.61-3.41 (m, 8H), 1.46 (s, 9H). Compound **430** was synthesized from amine **54** and bromide **429** using the same procedure as described for compound **4316**. LCMS (ESI) *m/e* 584 $(M+H)^+$. A solution of **430** (50 mg, 0.085 mmol) in CH_2Cl_2-CF_3COOH (1:1, 4 mL) was stirred at 0°C for 1h. The reaction mixture was concentrated and the crude product after purification (7:1:0.05 CH_2Cl_2/MeOH/NH_4OH) afforded 35 mg of compound **4314**. ^{1}HNMR (300 MHz, CD_3OD): δ 7.51-7.23 (m, 7H), 4.73-4.67 (m, 1H), 4.07 (t, J = 9 Hz, 1H), 3.75 (dd, J = 8, 3 Hz, 1H), 3.73 (s. 2H), 3.48-3.41 (m, 6H), 3.24 (s, 2H), 3.21-3.19 (m, 2H), 2.75-2.65 (m, 4H), 1.87 (s, 3H). LCMS (ESI) *m/e* 484 $(M+H)^+$.

Example 74 - Synthesis of Triazole 5001

Scheme 50 depicts the synthesis of triazole **5001**.

Scheme 50



Synthesis of triazole 501

A mixture of 1H-1,2,3-triazole-5-thiol sodium salt **502** (246 mg, 2 mmol) and 2-(Boc-amino)ethyl bromide **503** (448 mg, 2 mmol) in DMF (2 mL) was stirred at room temperature for 2 h. 50 mL of EtOAc was added and the solution was washed with water, dried over $MgSO_4$ and concentrated to afford 458 mg of triazole **501** as colorless oil in a yield of 94%. MS (ESI): 267.0 (100%) $(M+Na)^+$.

Synthesis of triazole 504

To a solution of triazole **501** (458 mg, 1.88 mmol) in CH_2Cl_2 (10 mL) and MeOH (2 mL) was added 4 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 2 h, the reaction was concentrated to dryness. The residue was dissolved in DMF (7 mL) and then chloride **90** (377 mg, 1 mmol) and Hunig's base (diisopropylethylamine, 0.8 mL, 4.6 mmol) were added. The solution was heated at 70 °C for 3 h. The DMF was removed *in vacuo*, and the residue was dissolved in a mixed solvent of THF (10 mL) and water (2 mL). K_2CO_3 (414 mg, 3 mmol) and di-tert-butyl dicarbonate (545 mg, 2.5 mmol) were then added, and the reaction was stirred at room temperature for 12 h. The THF was removed *in vacuo,* 50 mL of EtOAc was added, and the solution was washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by preparative thin layer chromatography (15:1:0.1 CH_2Cl_2/MeOH/ $NH_3 \cdot H_2O$) to afford 192 mg of triazole **504** in a yield of 33%. MS (ESI): 485.1 (100%), 607.2 $(M+Na)^+$.

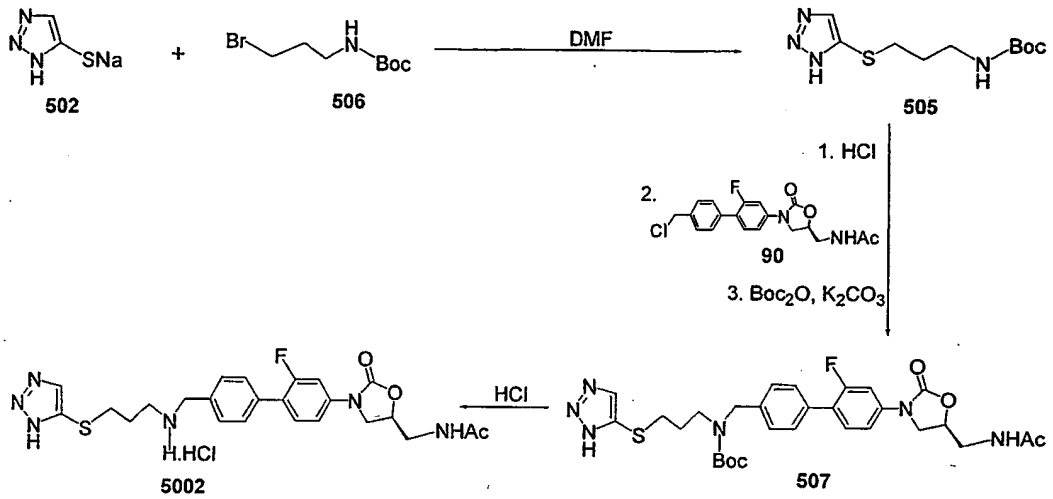
Synthesis of compound 5001

To a solution of triazole **504** (192 mg, 0.33 mmol) in CH_2Cl_2 (10 mL) and MeOH (2 mL) was added 4 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 12 h, the reaction was concentrated and washed with EtOAc/MeOH to give 150 mg of triazole **5001** in a yield of 94%. MS (ESI): 485.1(100%) $(M+H)^+$, 507.2 $(M+Na)^+$.

Example 75 - Synthesis of Triazole 5002

Scheme 51 depicts the synthesis of triazole **5002**.

Scheme 51



Synthesis of triazole 505

A mixture of 1H-1,2,3-triazole-5-thiol sodium salt **502** (246 mg, 2 mmol) and 2-(BOC-amino)propyl bromide **506** (476 mg, 2 mmol) in DMF (2 mL) was stirred at room temperature for 1 h. 50 mL of EtOAc was added and the solution was washed with water, dried over $MgSO_4$ and concentrated to afford 508 mg of triazole **505** as colorless oil in a yield of 98%. MS (ESI): 281.1 (100%, $(M+Na)^+$).

Synthesis of triazole 507

To a solution of triazole **505** (365 mg, 1.36 mmol) in CH_2Cl_2 (10 mL) and MeOH (2 mL) was added 4 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 2 h, the reaction was concentrated to dryness. The residue was dissolved in DMF (5 mL) and then chloride **90** (377 mg, 1 mmol) and Hunig's base (diisopropylethylamine, 0.52 mL, 3 mmol) were added. The solution was heated at 50 °C for 10 h. The DMF was removed *in*

vacuo and the residue was purified by preparative thin layer chromatography (10:1:0.1 CH_2Cl_2/MeOH/ $NH_3 \cdot H_2O$) to afford 230 mg of crude triazole **5002** (90% pure, MS (ESI): 499.1 (100%) $(M+H)^+$).

The free base of **5002** was dissolved in a mixed solvent of THF (10 mL) and water (2 mL), and K_2CO_3 (138 mg, 1 mmol) and di-tert-butyl dicarbonate (207 mg, 0.95 mmol) were then added. The reaction was stirred at room temperature for 12 h. The THF was removed *in vacuo*. 50 mL of EtOAc was added and the solution was washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by preparative thin layer chromatography (15:1:0.05 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 220 mg of triazole **507** in a yield of 37%. MS (ESI): 499.3 (100%), 621.1 $(M+Na)^+$.

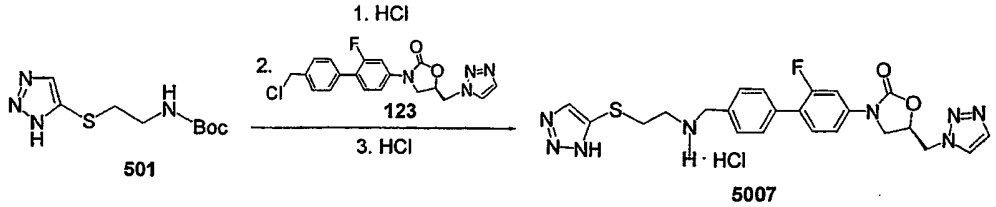
Synthesis of compound 5002

To a solution of **507** (98 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) and MeOH (1 mL) was added 2 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 12 h, the reaction was concentrated and washed with EtOAc/MeOH to give 78 mg of compound **5002** in a yield of 95%. MS (ESI): 499.1(100%, $(M+H)^+$).

Example 76 - Synthesis of Triazole 5007

Scheme 52 depicts the synthesis of triazole **5007**.

Scheme 52



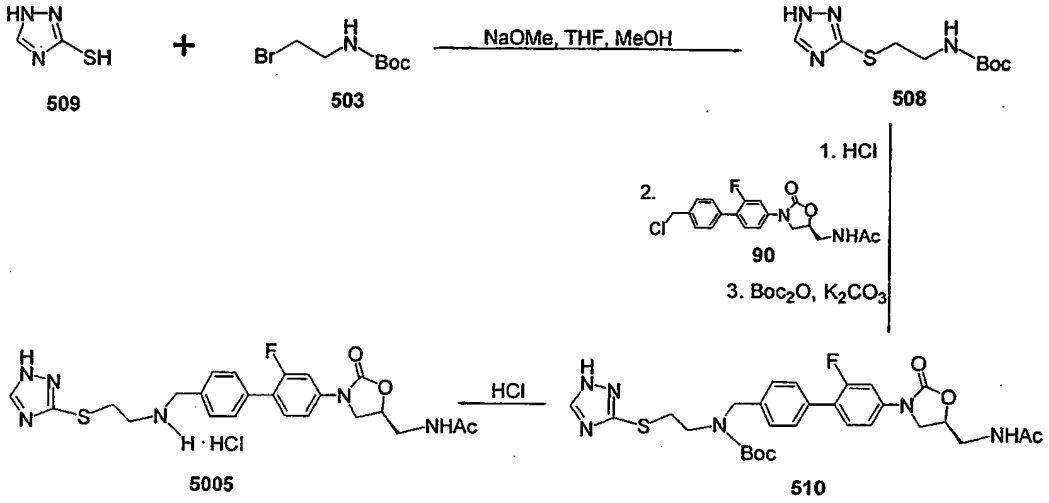
To a solution of triazole **501** (488 mg, 2 mmol) in CH_2Cl_2 (10 mL) and MeOH (2 mL) was added 4 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 2 h, the reaction was concentrated to dryness. The residue was dissolved in DMF (5 mL) and then chloride **123** (541 mg, 1.4 mmol) and diisopropylethylamine (0.7 mL, 4 mmol) were added. The solution was heated at 50 °C for 18 h. The DMF was removed *in vacuo* and the residue was purified by preparative thin layer chromatography (10:1:0.15 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 250 mg of compound **5007** in a yield of 36%. MS (ESI): 495.0 (100%) $(M+H)^+$.

The free base of compound **5007** was dissolved in CH_2Cl_2 (5 mL) and MeOH (5 mL). 2 mL of HCl solution (4.0 M in dioxane) was added at 0 °C. After stirring at room temperature for 1 h, the reaction was concentrated, washed with EtOAc/MeOH to give 260 mg of the HCl salt compound **5007** in a yield of 97%. MS (ESI): 495.1 (100%) $(M+H)^+$.

Example 77 - Synthesis of Triazole 5005

Scheme 53 depicts the synthesis of triazole **5005**.

Scheme 53



Synthesis of triazole 508

To a solution of 1H-1,2,4-triazole-3-thiol **509** (202 mg, 2 mmol) and 2-(BOC-amino)ethyl bromide **503** (448 mg, 2 mmol) in THF (5 mL) and MeOH (2 mL) was added a solution of NaOMe in MeOH (25% wt., 432 mg, 2 mmol). After stirring at room temperature for 2 h, 50 mL of EtOAc was added, and the solution was washed with water, dried over $MgSO_4$ and concentrated to afford 464 mg of triazole **508** as colorless oil in a yield of 95%. MS (ESI): 266.8 (100%) $(M+Na)^+$.

Synthesis of triazole 510

To a solution of triazole **508** (366 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) and MeOH (2 mL) was added 4 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 3 h, the reaction was concentrated to dryness. The residue was dissolved in DMF (5 mL) and then chloride **90** (377 mg, 1 mmol) and Hunig's base (diisopropylethylamine, 0.7 mL, 4 mmol) were added. The solution was heated at 50 °C for 12 h. The DMF was removed *in vacuo* and the residue was purified by preparative thin layer chromatography (10:1:0.15 CH_2Cl_2/MeOH/

$NH_3 \cdot H_2O$) to afford 250 mg of crude compound **5005** (85% pure, MS (ESI): 485.1 (100%) $(M+H)^+$)).

The crude **5005** was dissolved in a mixed solvent of THF (10 mL) and water (2 mL), and then K_2CO_3 (276 mg, 2 mmol) and di-tert-butyl dicarbonate (218 mg, 1 mmol) were added. The reaction was stirred at room temperature for 12 h. The THF was removed *in vacuo*. 50 mL of EtOAc was added and the solution was washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by preparative thin layer chromatography (15:1:0.1 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 150 mg of **510** in a yield of 26%. MS (ESI): 485.1 (100%), 607.1 $(M+Na)^+$.

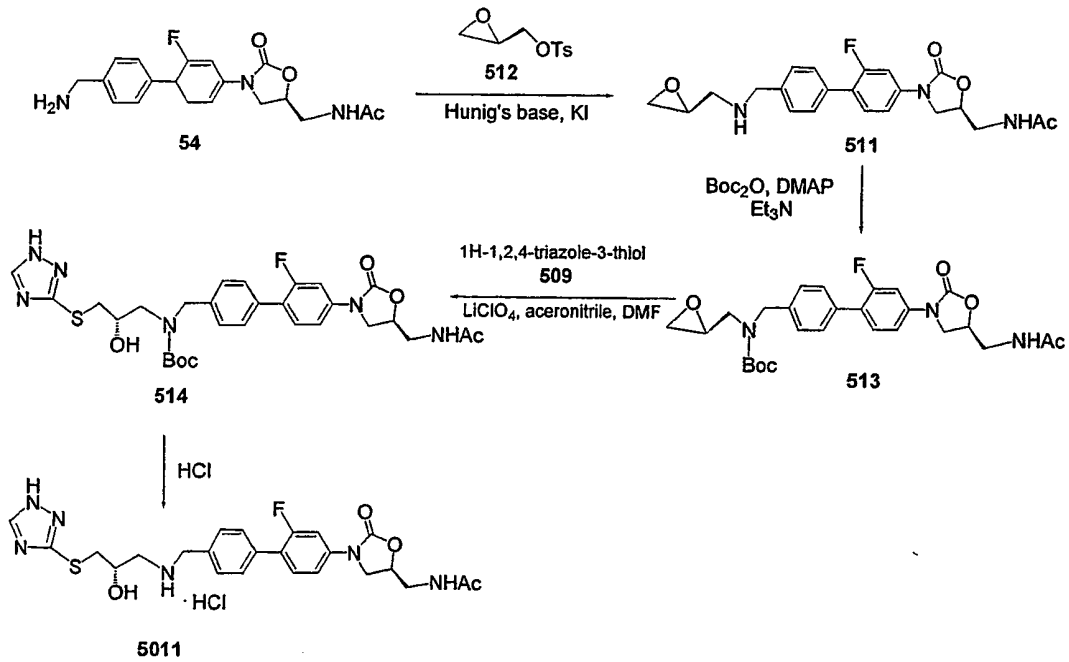
Synthesis of compound 5005

To a solution of triazole **510** (150 mg, 0.26 mmol) in CH_2Cl_2 (10 mL) and MeOH (2 mL) was added 2 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 12 h, the reaction was concentrated and washed with EtOAc/MeOH to give 120 mg of compound **5005** in a yield of 89%. MS (ESI): 485.1 (100%, $(M+H)^+$), 507.0 $(M+Na)^+$.

Example 78 - Synthesis of 5011

Scheme 54 depicts the synthesis of triazole **5011.**

Scheme 54



Synthesis of compound 511

A mixture of amine **54** (714 mg, 2 mmol), 2R-(-)-glycidyl tosylate **512** (456 mg, 2 mmol), N,N-diisopropylethylamine (0.44 mL, 2.5 mmol) and potassium iodide (33 mg, 0.2 mmol) in DMF (5 mL) was heated at 70 °C for 1 h. The reaction was diluted with 50 mL of EtOAc. The solution was washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by preparative thin layer chromatography (10:1:0.1 CH_2Cl_2/MeOH/ $NH_3 \cdot H_2O$) to afford 350 mg of compound **511** in a yield of 42%. MS (ESI): 414.1 (100%), 436.0 $(M+Na)^+$.

Synthesis of compound 513

To a solution of compound **511** (160 mg, 0.39 mmol) in THF (10 mL) and DMF (1 mL) was added di-tert-butyl dicarbonate (138 mg, 0.63 mmol), triethylamine (0.2 mL, 1.4 mmol) and N,N-dimethylaminopyridine. The reaction was stirred at room temperature for 1 h, and THF was removed *in vacuo*. 40 mL of EtOAc was added and the solution was washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by preparative thin layer chromatography (15:1:0.1 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 138 mg of compound **513** in a yield of 70%. MS (ESI): 514.1 (100%) $(M+H)^+$, 536.1 $(M+Na)^+$.

Synthesis of compound 514

To a solution of compound **513** (120 mg, 0.23 mmol) and $LiClO_4$ (27 mg, 0.25 mmol) in acetonitrile (2 mL) was added 1H-1,2,4-triazole-3-thiol **509** (24 mg, 0.23 mmol). The reaction was heated at 100 °C for 6 days and concentrated to dryness. The crude product was purified by preparative thin layer chromatography (15:1:0.1 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 75 mg of compound **514** in a yield of 53%. MS (ESI): 515.1 (100%), 615.1 $(M+H)^+$.

Synthesis of compound 5011

To a solution of compound **514** (75 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) and MeOH (1 mL) was added 1 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 24 h, the reaction was concentrated and washed with EtOAc/MeOH to give 62 mg of **5011** in a yield of 94%. MS (ESI): 515.1 (100%) $(M+H)^+$.

INCORPORATION BY REFERENCE

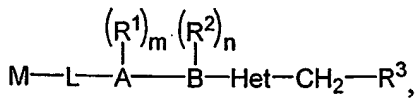
The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

WHAT IS CLAIMED IS:

1. A compound having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

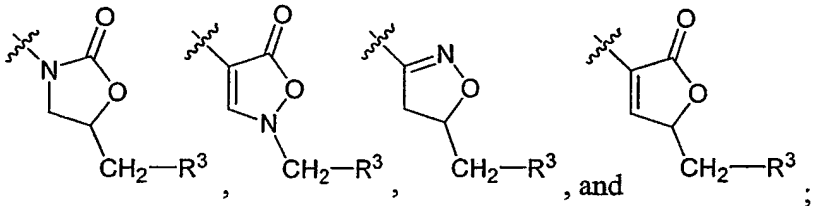
A is selected from the group consisting of:

phenyl, pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl;

B is selected from the group consisting of:

phenyl, pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl;

Het-CH_2-R^3 is selected from the group consisting of:



;

M is selected from the group consisting of:

a) saturated, unsaturated, or aromatic C_{3-14} carbocycle, and b) saturated, unsaturated, or aromatic 3-14 membered heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

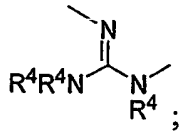
wherein a) or b) optionally is substituted with one or more R^5 groups;

M-L is selected from the group consisting of:

a) M-X, b) M-L^1, c) M-L^1-X, d) M-X-L^2, e) M-L^1-X-L^2, f) M-X-L^1-X-L^2, g) M-L^1-X-L^2-X, h) M-X-X-, i) M-L^1-X-X-, j) M-X-X-L^2, and k) M-L^1-X-X-L^2, wherein

X, at each occurrence, independently is selected from the group consisting of:

a) -O-, b) -NR^4-, c) –N(O)-, d) –N(OR^4)-, e) -$S(O)_p$-, f) -SO_2NR^4-, g) -NR^4SO_2-, h) -NR^4-N=, i) =N-NR^4-, j) -O-N=, k) =N-O-, l) -N=, m) =N-, n) -NR^4-NR^4-, o) -$NR^4C(O)O$-, p) -$OC(O)NR^4$-, q) -$NR^4C(O)NR^4$- r) -$NR^4C(NR^4)NR^4$-, and s)



;

L^1 is selected from the group consisting of:

a) C_{1-6} alkyl, b) C_{2-6} alkenyl, and c) C_{2-6} alkynyl,

wherein any of a) – c) optionally is substituted with one or more R^5 groups; and

L^2 is selected from the group consisting of:

a) C_{1-6} alkyl, b) C_{2-6} alkenyl, and c) C_{2-6} alkynyl,

wherein any of a) – c) optionally is substituted with one or more R^5 groups;

R^1, at each occurrence, independently is selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) $-CF_3$, f) $-OR^4$, g) -CN, h) $-NO_2$, i) $-NR^4R^4$, j) $-C(O)R^4$, k) $-C(O)OR^4$, l) $-OC(O)R^4$, m) $-C(O)NR^4R^4$, n) $-NR^4C(O)R^4$, o) $-OC(O)NR^4R^4$, p) $-NR^4C(O)OR^4$, q) $-NR^4C(O)NR^4R^4$, r) $-C(S)R^4$, s) $-C(S)OR^4$, t) $-OC(S)R^4$, u) $-C(S)NR^4R^4$, v) $-NR^4C(S)R^4$, w) $-OC(S)NR^4R^4$, x) $-NR^4C(S)OR^4$, y) $-NR^4C(S)NR^4R^4$, z) $-NR^4C(NR^4)NR^4R^4$, aa) $-S(O)_pR^4$, bb) $-SO_2NR^4R^4$, and cc) R^4;

R^2, at each occurrence, independently is selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) $-CF_3$, f) $-OR^4$, g) -CN, h) $-NO_2$, i) $-NR^4R^4$, j) $-C(O)R^4$, k) $-C(O)OR^4$, l) $-OC(O)R^4$, m) $-C(O)NR^4R^4$, n) $-NR^4C(O)R^4$, o) $-OC(O)NR^4R^4$, p) $-NR^4C(O)OR^4$, q) $-NR^4C(O)NR^4R^4$, r) $-C(S)R^4$, s) $-C(S)OR^4$, t) $-OC(S)R^4$, u) $-C(S)NR^4R^4$, v) $-NR^4C(S)R^4$, w) $-OC(S)NR^4R^4$, x) $-NR^4C(S)OR^4$, y) $-NR^4C(S)NR^4R^4$, z) $-NR^4C(NR^4)NR^4R^4$, aa) $-S(O)_pR^4$, bb) $-SO_2NR^4R^4$, and cc) R^4;

R^3 is selected from the group consisting of:

a) $-OR^4$, b) $-NR^4R^4$, c) $-C(O)R^4$, d) $-C(O)OR^4$, e) $-OC(O)R^4$, f) $-C(O)NR^4R^4$, g) $-NR^4C(O)R^4$, h) $-OC(O)NR^4R^4$, i) $-NR^4C(O)OR^4$, j) $-NR^4C(O)NR^4R^4$, k) $-C(S)R^4$, l) $-C(S)OR^4$, m) $-OC(S)R^4$, n) $-C(S)NR^4R^4$, o) $-NR^4C(S)R^4$, p) $-OC(S)NR^4R^4$, q) $-NR^4C(S)OR^4$, r) $-NR^4C(S)NR^4R^4$, s) $-NR^4C(NR^4)NR^4R^4$, t) $-S(O)_pR^4$, u) $-SO_2NR^4R^4$, and v) R^4;

R^4, at each occurrence, independently is selected from the group consisting of:

a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, g) -C(O)-C_{1-6} alkyl, h) -C(O)-C_{2-6} alkenyl, i) –C(O)-C_{2-6} alkynyl, j) -C(O)-C_{3-14} saturated, unsaturated, or aromatic carbocycle, k) -C(O)-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, l) -C(O)O-C_{1-6} alkyl, m) -C(O)O-C_{2-6} alkenyl, n) –C(O)O-C_{2-6} alkynyl, o) -C(O)O-C_{3-14} saturated, unsaturated, or aromatic carbocycle, and p) -C(O)O-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more R^5 groups;

R^5, at each occurrence, is independently selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) =O, f) =S, g) =NR^6, h) =NOR^6, i) =N-NR^6R^6, j) -CF_3, k) –OR^6, l) -CN, m) -NO_2, n) –NR^6R^6, o) -C(O)R^6, p) -C(O)OR^6, q) -OC(O)R^6, r) -C(O)NR^6R^6, s) –NR^6C(O)R^6, t) -OC(O)NR^6R^6, u) -NR^6C(O)OR^6, v) -NR^6C(O)NR^6R^6, w) -C(S)R^6, x) -C(S)OR^6, y) -OC(S)R^6, z) -C(S)NR^6R^6, aa) -NR^6C(S)R^6, bb) -OC(S)NR^6R^6, cc) -NR^6C(S)OR^6, dd) –NR^6C(S)NR^6R^6, ee) –NR^6C(NR^6)NR^6R^6, ff) -$S(O)_pR^6$, gg) -$SO_2NR^6R^6$, and hh) R^6;

R^6, at each occurrence, independently is selected from the group consisting of:

a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, g) -C(O)-C_{1-6} alkyl, h) -C(O)-C_{2-6} alkenyl, i) –C(O)-C_{2-6} alkynyl, j) -C(O)-C_{3-14} saturated, unsaturated, or aromatic carbocycle, k) -C(O)-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, l) -C(O)O-C_{1-6} alkyl, m) -C(O)O-C_{2-6} alkenyl, n) –C(O)O-C_{2-6} alkynyl, o) -C(O)O-C_{3-14} saturated,

unsaturated, or aromatic carbocycle, and p) -C(O)O-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more R^7 groups;

R^7, at each occurrence, independently is selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) =O, f) =S, g) $=NR^8$, h) $=NOR^8$, i) $=N\text{-}NR^8R^8$, j) $-CF_3$, k) $-OR^8$, l) -CN, m) $-NO_2$, n) $-NR^8R^8$, o) $-C(O)R^8$, p) $-C(O)OR^8$, q) $-OC(O)R^8$, r) $-C(O)NR^8R^8$, s) $-NR^8C(O)R^8$, t) $-OC(O)NR^8R^8$, u) $-NR^8C(O)OR^8$, v) $-NR^8C(O)NR^8R^8$, w) $-C(S)R^8$, x) $-C(S)OR^8$, y) $-OC(S)R^8$, z) $-C(S)NR^8R^8$, aa) $-NR^8C(S)R^8$, bb) $-OC(S)NR^8R^8$, cc) $-NR^8C(S)OR^8$, dd) $-NR^8C(S)NR^8R^8$, ee) $-NR^8C(NR^8)NR^8R^8$, ff) $-S(O)_pR^8$, gg) $-SO_2NR^8R^8$, hh) C_{1-6} alkyl, ii) C_{2-6} alkenyl, jj) C_{2-6} alkynyl, kk) C_{3-14} saturated, unsaturated, or aromatic carbocycle, and ll) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of hh) – ll) optionally is substituted with one or more moieties selected from the group consisting of R^8, F, Cl, Br, I, $-CF_3$, $-OR^8$, $-SR^8$, -CN, $-NO_2$, $-NR^8R^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-C(O)NR^8R^8$, $-NR^8C(O)R^8$, $-OC(O)NR^8R^8$, $-NR^8C(O)OR^8$, $-NR^8C(O)NR^8R^8$, $-C(S)R^8$, $-C(S)OR^8$, $-OC(S)R^8$, $-C(S)NR^8R^8$, $-NR^8C(S)R^8$, $-OC(S)NR^8R^8$, $-NR^8C(S)OR^8$, $-NR^8C(S)NR^8R^8$, $-NR^8C(NR^8)NR^8R^8$, $-SO_2NR^8R^8$, and $-S(O)_pR^8$;

R^8, at each occurrence, independently is selected from the group consisting of:

a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, g) $-C(O)\text{-}C_{1-6}$ alkyl, h) $-C(O)\text{-}C_{2-6}$ alkenyl, i) $-C(O)\text{-}C_{2-6}$ alkynyl, j) $-C(O)\text{-}C_{3-14}$ saturated, unsaturated, or aromatic carbocycle, k) -C(O)-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, l) $-C(O)O\text{-}C_{1-6}$ alkyl,

m) -C(O)O-C_{2-6} alkenyl, n) –C(O)O-C_{2-6} alkynyl, o) -C(O)O-C_{3-14} saturated, unsaturated, or aromatic carbocycle, and p) -C(O)O-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more moieties selected from the group consisting of F, Cl, Br, I, -CF_3, -OH, -OCH_3, -SH, -SCH_3, -CN, -NO_2, –NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$C(O)CH_3$, -$C(O)OCH_3$, -$C(O)NH_2$, –$NHC(O)CH_3$, -SO_2NH_2, -SO_2NHCH_3, -$SO_2N(CH_3)_2$, and-$S(O)_pCH_3$;

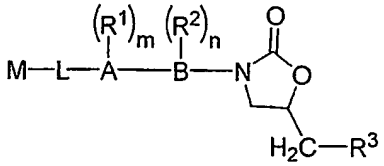
m, at each occurrence, independently is 0, 1, 2, 3, or 4;

n, at each occurrence, independently is 0, 1, 2, 3, or 4; and

p, at each occurrence, independently is 0, 1, or 2,

and wherein the compound does not have the formula corresponding to any of the structures listed in Table 1.

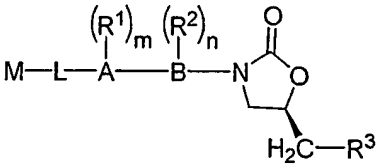
2. The compound according to claim 1, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein A, B, L, M, R^1, R^2, R^3, m, and n are defined as described in claim 1.

3. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein A, B, L, M, R^1, R^2, R^3, m, and n are defined as described in claim 1.

4. The compound according to any one of claims 1-3, wherein

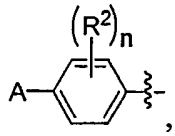
A is selected from the group consisting of phenyl and pyridyl;

B is selected from the group consisting of phenyl and pyridyl;

m is 0, 1, or 2; and

n is 0, 1, or 2.

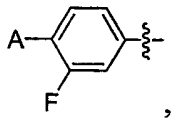
5. The compound according to any one of claims 1-4, wherein A-B is:



,

wherein A, R^2, and n are defined as described in claim 1.

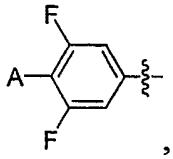
6. The compound according to claim 5, wherein A-B is:



,

wherein A is defined as described in claim 1.

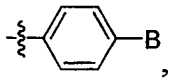
7. The compound according to claim 5, wherein A-B is:



,

wherein A is defined as described in claim 1.

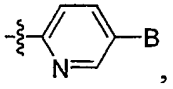
8. The compound according to any one of claims 1-7, wherein A-B is:



,

wherein B is defined as described in claim 1.

9. The compound according to any one of claims 1-7, wherein A-B is:



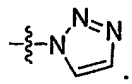
,

wherein B is defined as described in claim 1.

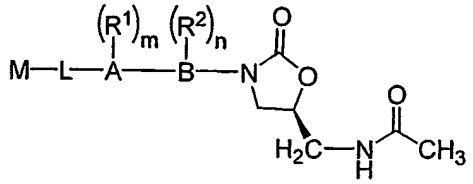
10. The compound according to any one of claims 1-9, wherein R^3 is $-NHC(O)R^4$.

11. The compound according to claim 10, wherein R^4 is $-CH_3$.

12. The compound according to any one of claims 1-9, wherein R^3 is:



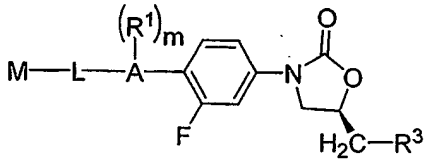
13. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein A, B, L, M, R^1, R^2, m, and n are defined as described in claim 1.

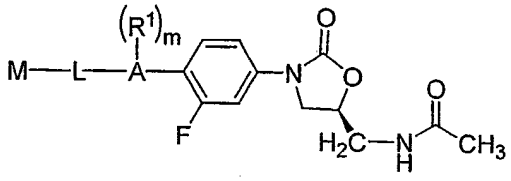
14. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein A, L, M, R^1, R^3, and m are defined as described in claim 1.

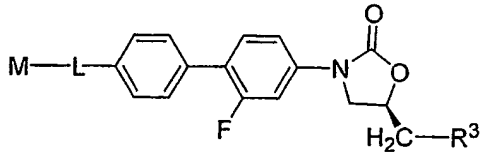
15. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein A, L, M, R^1, and m are defined as described in claim 1.

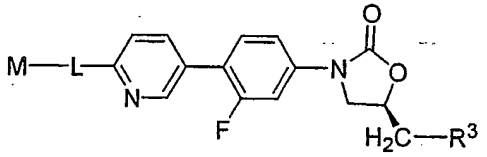
16. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein L, M, and R^3 are defined as described in claim 1.

17. The compound according to claim 1 or 2, having the formula:

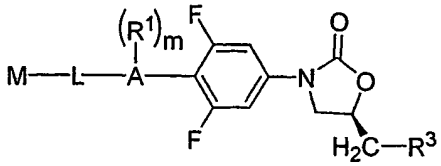


or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein L, M, and R^3 are defined as described in claim 1.

18. The compound according to claim 16 or 17, wherein R^3 is $-NHC(O)CH_3$.

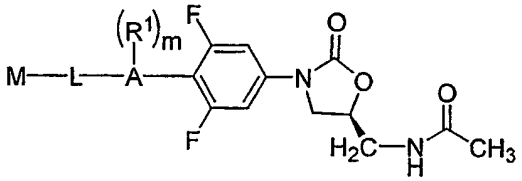
19. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein A, L, M, R^1, R^3, and m are defined as described in claim 1.

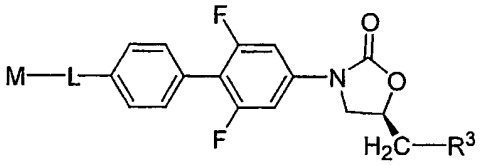
20. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein A, L, M, R^1, and m are defined as described in claim 1.

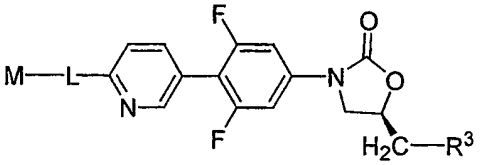
21. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein L, M, and R^3 are defined as described in claim 1.

22. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein L, M, and R^3 are defined as described in claim 1.

23. The compound according to claim 21 or 22, wherein R^3 is $-NHC(O)CH_3$.

24. The compound according to any one of claims 1-23, wherein

M-L is M-L^1, and

L^1 is C_{1-6} alkyl.

25. The compound according to claim 24, wherein M-L^1 is:

M–CH_2-.

26. The compound according to any one of claims 1-23, wherein

M-L is M-L^1-X-L^2, and

X is -NR^4-.

27. The compound according to claim 26, wherein X is –NH-.

28. The compound according to claim 26, wherein X is:

29. The compound according to claim 26, wherein X is –N(O)-.

30. The compound according to claim 26, wherein X is –N(OR^4)-.

31. The compound according to claim 30, wherein R^4 is H.

32. The compound according to claim 30, wherein R^4 is C_{1-6} alkyl.

33. The compound according to claim 26, wherein

L^1 is C_{1-6} alkyl, and

L^2 is C_{1-6} alkyl.

34. The compound according to claim 33, wherein

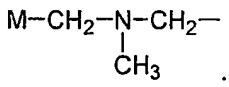
L^1 is –CH_2-, and

L^2 is -CH_2-.

35. The compound according to claim 26, wherein M-L is:

M-CH_2-NH-CH_2-.

36. The compound according to claim 26, wherein M-L is:



37. The compound according to any one of claims 1-23, wherein

M-L is M-S-L^1-NR^4- L^2,

L^1 is C_{1-6} alkyl, and

L^2 is C_{1-6} alkyl.

38. The compound according to claim 37, wherein M-L is:

M-S–CH_2CH_2-NH-CH_2-.

39. The compound according to any one of claims 1-38, wherein M is selected from the group consisting of:

a) phenyl, b) pyridyl, c) pyrazinyl, d) pyrimidinyl, e) pyridazinyl, f) oxiranyl, g) aziridinyl, h) furanyl, i) thiophenyl, j) pyrrolyl, k) oxazolyl, l) isoxazolyl, m) imidazolyl, n) pyrazolyl, o) isothiazolyl, p) thiazolyl, q) triazolyl, r) tetrazolyl, s) indolyl, t) purinyl, u) benzofuranyl, v) benzoxazolyl, w) benzisoxazolyl, x) quinolinyl, y) isoquinolinyl, z) quinoxalinyl, aa) quinazolinyl, bb) cinnolinyl, cc) cyclopropyl, dd) cyclobutyl, ee) cyclopentyl, ff) cyclohexyl, gg) cycloheptyl, hh) oxetanyl, ii) tetrahydrofuranyl, jj) tetrahydropyranyl, kk) azetidinyl, ll) pyrrolidinyl, mm) piperidinyl, nn) thietanyl, oo) tetrahydrothiophenyl, pp) tetrahydrothiopyranyl, qq) piperazinyl, rr) quinuclidinyl, ss) 1-azabicyclo[2.2.1]hyeptanyl, tt) morpholinyl, uu) thiomorpholinyl, vv) thiooxomorpholinyl, ww) thiodioxomorpholinyl, and xx) benzothiophenyl

wherein any of a) – xx) optionally is substituted with one or more R^5 groups.

40. The compound according to claim 39, wherein M is 4-isoxazolyl.

41. The compound according to claim 39, wherein M is [1,2,3]triazol-1-yl.

42. The compound according to claim 39, wherein M is 3H-[1,2,3]triazol-4-yl.

43. The compound according to claim 39, wherein M is 1H-tetrazol-5-yl.

44. The compound according to claim 39, wherein M is piperidin-1-yl.

45. The compound according to claim 39, wherein M is pyrolidin-1-yl.

46. A compound having the structure corresponding to any one of the structures listed in Table 2, or a pharmaceutically acceptable salt, ester, or prodrug thereof.

47. A pharmaceutical composition comprising one or more compounds according to any one of claims 1-46 and a pharmaceutically acceptable carrier.

48. A method of treating a microbial infection in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46.

49. A method of treating a fungal infection in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46.

50. A method of treating a parasitic disease in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46.

51. A method of treating a proliferative disease in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46.

52. A method of treating a viral infection in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46.

53. A method of treating an inflammatory disease in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46.

54. A method of treating a gastrointestinal motility disorder in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46.

55. A method of treating a disorder in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46 thereby to ameliorate a symptom of the disorder, wherein the disorder is selected from the group consisting of:

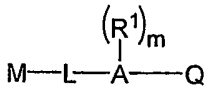
a skin infection, nosocomial pneumonia, post-viral pneumonia, an abdominal infection, a urinary tract infection, bacteremia, septicemia, endocarditis, an atrio-ventricular shunt infection, a vascular access infection, meningitis, surgical prophylaxis, a peritoneal infection, a bone infection, a joint infection, a methicillin-resistant *Staphylococcus aureus* infection, a vancomycin-resistant *Enterococci* infection, a linezolid-resistant organism infection, and tuberculosis.

56. The method according to any one of claims 48-55, wherein the compound is administered orally, parentally, or topically.

57. A medical device containing one or more compounds according to any one of claims 1-46.

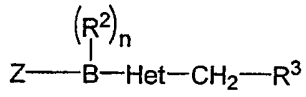
58. The medical device according to claim 57, wherein the device is a stent.

59. A process for preparing a compound according to claim 1, comprising the step of reacting a compound of formula (I):



(I)

with a compound of formula (II):



(II)

in a solvent in the presence of a base and a palladium catalyst, wherein

Q is a boronate having the formula $-BY_2$, wherein

Y, at each occurrence, independently is selected from the group consisting of:

a) –OH, and b) $-O-C_{1-4}$ alkyl,

alternatively, two Y groups taken together are selected from the group consisting of:

a) $-OC(R^4)(R^4)C(R^4)(R^4)O-$, and b) $-OC(R^4)(R^4)CH_2C(R^4)(R^4)O-$,

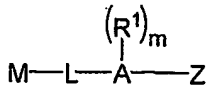
alternatively, two Y groups taken together with the boron to which they are bound comprise a BF_3 alkali metal salt;

Z is selected from the group consisting of:

a) I, b) Br, c) Cl, and d) R^4OSO_3-; and

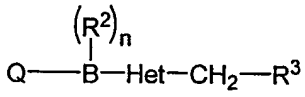
A, B, L, M, R^1, R^2, R^3, R^4, m, and n are defined as described in claim 1.

60. A process for preparing a compound according to claim 1, comprising the step of reacting a compound of formula (I):



(I)

with a compound of formula (II):



(II)

in a solvent in the presence of a base and a palladium catalyst, wherein

Q is a boronate having the formula $-BY_2$, wherein

Y, at each occurrence, independently is selected from the group consisting of:

a) –OH, and b) $-O-C_{1-4}$ alkyl,

alternatively, two Y groups taken together are selected from the group consisting of:

a) $-OC(R^4)(R^4)C(R^4)(R^4)O-$, and b) $-OC(R^4)(R^4)CH_2C(R^4)(R^4)O-$,

alternatively, two Y groups taken together with the boron to which they are bound comprise a BF_3 alkali metal salt;

Z is selected from the group consisting of:

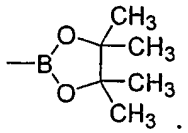
a) I, b) Br, c) Cl, and d) R^4OSO_3-; and

A, B, L, M, R^1, R^2, R^3, R^4, m, and n are defined as described in claim 1.

61. The process according to claim 59 or 60, wherein Z is I.

62. The process according to any one of claims 59-61, wherein Q is $-BF_2 \cdot KF$.

63. The process according to any one of claims 59-61, wherein Q is:



64. The process according to any one of claims 59-63, wherein the base is selected from the group consisting of an alkali metal hydroxide, an alkali metal carbonate, an alkali metal fluoride, a trialkyl amine, and mixtures thereof.

65. The process according to claim 64, wherein the base is selected from the group consisting of potassium carbonate, sodium carbonate, potassium fluoride, triethylamine, diisopropylethylamine, and mixtures thereof.

66. The process according to claim 64, wherein the ratio of equivalents of base to equivalents of compound (I) is about 3:1.

67. The process according to any one of claims 59-66, wherein the palladium catalyst is a ligand coordinated palladium (0) catalyst.

68. The process according to claim 67, wherein the palladium catalyst is a tetrakis(trialkylphosphine) palladium (0) or a tetrakis(triarylphosphine) palladium (0) catalyst.

69. The process according to claim 68, wherein the palladium catalyst is tetrakis(triphenylphosphine) palladium (0).

70. The process according to claim 67, wherein the ratio of the equivalents of palladium catalyst to the equivalents of compound (I) is about 1:20.

71. The process according to any one of claims 59-70, wherein the solvent comprises an aqueous solvent.

72. The process according to any one of claims 59-70, wherein the solvent comprises a mixture of water and an organic solvent, wherein the organic solvent is selected from the group consisting of:

methanol, ethanol, propanol, isopropanol, butanol, isobutanol, secondary butanol, tertiary butanol, benzene, toluene, tetrahydrofuran, dimethylformamide, 1,2-diethyl ether, dimethoxyethane, diisopropyl ether, methyltertiarybutyl ether, methoxymethyl ether, 2-methoxyethyl ether, 1,4-dioxane, 1,3-dioxolane, and mixtures thereof.

73. The process according to claim 72, wherein the solvent comprises a mixture of water, toluene, and ethanol.

74. The process according to claim 73 wherein the solvent comprises a mixture of water, toluene, and ethanol in a ratio of about 1:3:1 by volume.

75. The process according to any one of claims 59-74, wherein the process is carried out at a temperature between about 20 °C and about 100 °C.

76. The process according to any one of claims 59-74, wherein the process is carried out at the reflux temperature of the solvent.